COGNITIVE DOMAINS FUNCTION COMPLEMENTATION BY *NTNG* GENE PARALOGS

Pavel Prosselkov[1,2]*, Denis Polygalov[3], Qi Zhang[1], Thomas J. McHugh[3], and Shigeyoshi Itohara[1]*

[1]Laboratory of Behavioral Genetics, RIKEN Brain Science Institute, Wakoshi, 351-0198 Saitama, Japan

[2]Graduate School, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University, 113-8657 Tokyo, Japan

[3]Laboratory of Circuit and Behavior Physiology, RIKEN Brain Science Institute, 351-0198 Saitama, Japan

*corresponding authors:

prosselkov@brain.riken.jp

sitohara@brain.riken.jp

Keywords: gene duplication, evolution, subfunctionalisation, cognitive complement

ABSTRACT

Gene duplication was proposed by S.Ohno (Ohno, 1970) as a key mechanism of a gene function evolution. A pair of gene paralogs, *NTNG1* and *NTNG2*, sharing identical gene and protein structures and encoding similar proteins, forms a functional complement subfunctionalising (SF) within cognitive domains and forming cognitive endophenotypes, as detected by Intellectual Quotient (IQ) tests (Prosselkov et al., 2015). *NTNG* paralogs are associated with autism spectrum disorder (ASD), bipolar disorder (BD) and schizophrenia (SCZ), with unique non-overlapping segregation among the other 15 cognitive disorders (CD), emphasizing an evolutionary gain-dependent link between advanced cognitive functions and concomitant cognitive pathologies. Complementary expression and human brain transcriptome composition of the paralogs explains the observed phenomena of their functional complementarity. The lowest identity among *NTNGs* is found in a middle of encoded by them proteins designated as uknown (Ukd) domain. *NTNG1* contains anthropoid-specific constrained regions and both genes contain non-coding conserved sequences underwent accelerated evolution in human. *NTNG* paralogs SF perturbates "structure drives function" concept at protein and gene levels. Their function diversification results in a so-called "Cognitive Complement (CC)" formation, a product of gene duplication and subsequent cognitive subfunction bifurcation among the *NTNG* gene duplicates.

INTRODUCTION

Gene duplication was proposed by S.Ohno (**Ohno, 1970**) as a key mechanism of a gene function evolution. Complex behaviors arise from a combination of simpler genetic modules that either have evolved separately or co-evolved. Many genes and the proteins they encode have been found to be involved in the cognitive information processing with a single variant or a single gene generally accounting for only a partial phenotypic variation in a complex trait. Cognitive processing as a quintessence of the brain functioning can be viewed as a product of intricately interlinked networks generated by deeply embedded into it players with specific or partially overlapping functions. The robustness of the cognitive processing towards its single elements genetic eliminations (to study their function) and its simultaneous fragility expressed in the multiple forms of neurological disorders manifest the existence of cognitive domains interlocked but SF within a unit of cognition formed upon these domains interaction. Previously, we have described a function of a pair of gene paralogs (*NTNG1* and *NTNG2*) involved in human IQ tests performance and underwent hominin-specific evolutionary changes (**Prosselkov et al., 2015**). Hereby, we continue looking at these genes paralogs features focusing on underlying mechanisms of their function segregation and complementation within the cognitive domains.

RESULTS

The previously observed phenomena of functional complementation among the *NTNG* paralogs within cognitive domains (**Prosselkov et al., 2015**) is also manifested in *NTNG*-associated human pathologies diagnosed in most cases (if only not in all) by a cognitive decline (**Figure 1A-1** and **A-2**). Both genes are associated with BD and SCZ – devastating disorders sharing similar etiology (**Lee et al., 2013**) with genetic correlation by multivariate analysis of 0.590 (**Maier et al., 2015**), linked to human creativity (**Power et al., 2015**), and characterized by impulsiveness as a common diagnostic feature (**Reddy et al., 2014**). Recently found associations of both paralogs with ASD (**Sanders et al., 2015**) supports the reported genetic correlation of 0.194 ASD/SCZ pair (**Maier et al., 2015**) and shared module eigengenes detected by PC1 among these two disorders (**Parikshak et al., 2015**). 12 *NTNG1*-linked CDs, ranging from AD to TS, span a broad spectrum of clinical features frequently involving reduced processing speed (PS) and verbal comprehension (VC, **Figure 1A-1**). As for *NTNG2*, working memory (WM) deficit and inability "to bind" events (perceptual organization, PO) are the most prominent diagnostic traits for the SLE and TLE patients (**Figure 1A-2**), with PN characterised by indolent behavior in 90% of the cases (**Cavard et al., 2009**). Thus, both *NTNG* paralogs are associated with a variety of CDs and mostly in a non-overlapping manner, except for ASD, BD and SCZ characterized by shared and wide spectrum of cognitive abnormalities. The clinical etiology of the aforementioned diseases supports the IQ-deduced functional complementation among the *NTNG* paralogs (**Prosselkov et al., 2015**) with (VC/PS) and (WM/PO) deficits being also uniquely segregated among the associated cognitive pathologies.

Since both genes are expected to have identical gene exon/intron compositions but different in their intron lengths (**Yin et al., 2002**) we have reconstructed the paralogs transcriptomes by re-processing the publicly available RNA-seq dataset (**Wu et al., 2012**)

from healthy and SCZ human subjects superior temporal gyrus (STG) post-mortem brain tissue (Supplementary Table 1a=**ST1a**). A difference is noted instantly at the total expression levels (genes, exons, individual RNA transcripts) when two gene paralogs are compared (**Figure 1B-1** and **B-2**). *NTNG2* amount (as a whole gene) is 5 times larger comparing to *NTNG1*; exons (2-5) are 3 times, exons (8-9) are 18 times and exon 10 is 4 times higher expressed for *NTNG2* than for *NTNG1*. The only two exons outlaying the prevailing amount rule for the *NTNG2* mRNAs are exons 6 and 7, expressed nearly at the same absolute level as for the *NTNG1* exon paralogs, making them highly underrepresented within the whole *NTNG2* transcriptome. Next, distinct non-alternating splicing modules are formed by exons (2-5) for *NTNG1* (**Figure 1B-1**), while exons (4-5) and exons (8-9) for *NTNG2* (**Figure 1B-2**). Two structurally identical RNA transcript paralogs (*NTNG1a* = G1a and *NTNG2a* = G2a) have been found to exist in both *NTNG* transcriptomes with G2a being expressed at 8-9 times higher level than G1a. *NTNG1* is uniformly presented across the all analysed 16 human samples by 2 more protein coding RNAs (G1c and G1d, detected previously in mice brain, **Nakashiba et al., 2000**) and by 2 non-coding intron (9-10) derived transcripts (**Figure 1B-1**). At the same time, *NTNG2* transcriptome is comprised of one extra potentially coding RNA (G2a-like with exon 2 spliced out but in-frame coding preserved) and 2 assumed to be non-coding RNAs with exons 6 and 7 retained along with preceding and following them introns. Quite interesting that these two latter transcripts are the only RNA species with *NTNG2* exon 6 and 7 retained (**Figure 1B-2**). Two more coding (G1f and G1n) and 4 more non-coding for *NTNG1* and 9 extra non-coding for *NTNG2* RNA species have been also assembled from the available reads but due to inconsistency in their appearance across all 16 STG samples they are not presented on the figure but summarized in the table (**Figure 1C**, for details refer to **ST1d**). Summarising above said, it can be concluded that quantitative and qualitative complementary differences is a prominent feature characterising the brain RNA

105 transcriptome of human *NTNG* paralogs. However, no significant changes at the
106 transcription level of neither whole genes, nor individual exons, nor reconstructed RNA
107 transcripts have been found for SCZ and healthy subjects.

108 Upon calling the presence of IQ-affecting SNPs (**Prosselkov et al., 2015**) across all
109 STG samples (**ST1c**) it has been revealed that 15 out of 16 subjects were positive for the T-
110 allele of rs2149171 (exon 4-nested), shown above to attenuate the WM score in SCZ patients,
111 making a comparison among the allele carrier *vs* non-carrier impossible. Four healthy and
112 three SCZ samples carry a T-allele of rs3824574 (exon 3-nested, non-affecting IQ), and 1
113 healthy and 1 SCZ sample each contains a C-allele of rs4915045 (exon10, non-coding part-
114 nested, and non-affecting IQ). Thus, among the eleven cognitive endophenotype-associated
115 SNPs only 3 were possible to call out of the available *NTNG* transcriptome.

116 Distinctly complementary nature of the *NTNG* paralogs segregation within
117 neurological disorders and RNA transcriptome usage in STG (**Figure 1**) has prompted us to
118 analyse both genes expression across the entire human brain. We have reconstructed both
119 genes expression profiles in the human brain areas over the life span from conception (pcw =
120 post-conception week) to mature age (30-40 yrs old) using the RNA-seq data from BrainSpan
121 (www.brainspan.org). Similarities and differences are easily noted when the age-dependent
122 phases of *NTNG1* and *NTNG2* expression profiles are matched (**Figure 2**). Based on the
123 visual inputs three distinct classifiers have been elaborated: 1. predominantly synchronous
124 (**Figure 2A(1-4))**, characteristic mostly for the cortical areas; 2. predominantly mixed and
125 asynchronous (**Figure 2B**), characteristic for the cerebellar cortex and subcortical formations;
126 and 3. anti-phasic (complementary, **Figure 2C**), characteristic for the MD of thalamus and
127 hippocampus. All analysed brain areas demonstrated an elevated level of *NTNG2* expression
128 in comparison to *NTNG1* except for thalamus (**Figure 2C**) with the largest difference
129 observed is at the time of birth (35-37 pcw) or soon after (4 mo) for the synchronous

130 classifiers (**Figure 2A**), oscillating increment values across the life span for the mixed
131 (**Figure 2B**) and anti-phasic (**Figure 2C**) classifiers. It is quite intriguing to note that
132 essentially all brain areas show a trend towards the expression difference being negated
133 between the paralogs by reaching the mature age of 30-40 yrs old (nearly or above the mean
134 age used for the IQ testing), except MD where the expression discrepancy is increased. Thus,
135 the observed functional complementation among the *NTNG* paralogs is supported by the
136 anatomical distribution of the genes in human brain and their expression pattern modality
137 over the human subjects lifetime.

138 A direct comparison of the *NTNG* paralogs shows not only identical intron-exon gene
139 structure (**Figure 1B-1, 2B-2**) but also closely matched exon sizes (**Figure 3A**). There are
140 three exons of identical sizes (exons 4, 8 and 9), another three exons differed by one encoded
141 aa (exons 3, 5 and 6) and there are exons of different sizes (exons 2, 7 and 10). In terms of
142 size the largest difference among the genes is visually presented by the introns: intron (9-10)
143 of *NTNG1* is 52.7 times larger its *NTNG2* paralogous intron with intron (6-7) of *NTNG1*
144 being only 1.43-times larger pointing towards non-equilibria process of non-coding elements
145 elaborations as the process of gene paralogs SF proceeded. Nevertheless, it can be
146 generalised that in average all *NTNG1* introns are several times larger their *NTNG2* analogs
147 (**Figure 3A**). We have shown previously that exons 6 and 7 are differentially used within the
148 brain *NTNG* transcriptome (**Figure 1B-1** and **B-2**) and to explore their potential contribution
149 into the paralogs SF we have built identity matrices with these exons excluded and included
150 (but still producing in-frame existing transcripts, **Figure 3B-1** left and right panels,
151 respectively). Exclusion of both exons from the full-lengths transcripts (thus converting
152 *NTNG1m* to *NTNG1a* and *NTNG2b* to *NTNG2a*, respectively) increases the identity of DNA
153 on 2% (a relatively large effect since both exons together represent only 7.22 and 9.69% of
154 the total coding part of the full-length RNA transcripts, *NTNG1m* and *NTNG2b*, respectively).

155 This effect becomes even stronger when the encoded by these transcripts proteins are also
156 compared (**Figure 3B-2**). The spliced out Ukd protein domains (encoded by the exons 6 and
157 7) increases the proteins identity on 3.8% thus making the middle of both genes (and encoded
158 proteins) substantially more different among the both gene paralogs. To corroborate this
159 observation and to explore the importance of other protein parts we have directly compared
160 the sequences encoded by the full-length transcripts and producing Netrin-G1m and Netrin-
161 G2b (**Figure 3C**). Similarly to what has been shown on **Figure 3B-1** and **3B-2**, the lowest
162 identity (17.5%) is represented by the Ukd domain (encoded by the exons 6 and 7) and by the
163 preceding it exon 5 (a 3'-part of the LE1 domain). Two other areas also show a substantially
164 low identity, namely the N-terminus (it includes the protein secretory signal indicated by an
165 arrow) and the outmost C-terminus responsible for the unique feature of Netrin-Gs – the GPI
166 attachment. Thus, based on the percent identity comparisons among the Netrin-G paralogs it
167 can be predicted that there are several potential protein parts contributing to the paralogs SF.
168 As it has been reported by **Seiradake et al. (2011)**, identical gene and protein domain
169 compositions result in the identical structural motif with differences only in the spatial
170 arrangement of the loops facing the post-synaptic Netrin-G's interacting partners, NGL-1 and
171 NGL-2, respectively (**Figure 3D**). Loop I binding surfaces alignment (**Figure 3C**, blue color)
172 shows a high level of conservation (with at least 5 amino acids 100% conserved) among the
173 Netrin-G paralogs, indicating that it is unlikely to be responsible for the cognate ligand
174 binding specificity. Neither Loop II (**Figure 5C**, yellow color) nor Loop III (**Figure 5C**,
175 orange color) display a single conserved amino acid shared among the paralogous binding
176 interfaces (as it originally has been described in **Seiradake et al., 2011**). Thus the
177 complementary pattern of the pre-postsynaptic interactions mediated via specific Netrin-
178 G/NGL pairs is reflected in the reciprocally different sizes of the loops binding interfaces
179 representing another element of the *NTNG*-encoded protein paralogs SF.
180

DISCUSSION

Complementary contribution of *NTNG* paralogs into human cognitive pathologies. Involvement of the pre-synaptically expressed axon-localised *NTNGs* in SCZ diagnosis supports the established view of SCZ as a result of distorted trans-synaptic signaling (**Lips et al., 2012**), with a recent study proving that axonal connectivity-associated genes form a functional network visualisable by fMRI (**Richiardi et al., 2015**), and that brain connectivity predicts the level of fluid intelligence (**Finn et al., 2015; Pamplona et al., 2015**). Both *NTNGs* have been found to participate in the brain functional connectivity by the parcellated connectome reconstruction ((**Hawrylycs et al., 2015**). Most of the reported disease associations link *NTNG1* to SCZ with a variety of other neurologic pathologies (15 in total, **Figure 1A-1**), while *NTNG2* pathologic associations (6 in total, **Figure 1A-2**) are quite limited to those affecting WM or PO. Among them is SLE frequently characterized by WM deficit (**Shucard et al., 2011**) and also known to represent schizoid-type abnormalities characteristic for autoimmune pathologies (**Guilloux et al., 2010**; **Eaton et al., 2006**). Immune activation is known to lead to altered pre-pulse inhibition (a key diagnostic trait for SCZ) reversed by antipsychotics (**Romero et al., 2007**). The three diseases associated with both paralogs (ASD, BD and SCZ) are also a primary focus of the recently initiated PsychENCODE project (**PsychENCODE et al., 2015**). It is also worth to mention the resemblance of the reported disease associations with the behavioral phenotypes of *Ntng1* and *Ntng2* gene knockout mice (**Qi et al., in press**).

It is a known fact that a gene content associated with IQ score often relates to numerous diseases, such as SCZ, ASD, depression, and others (see **Zhao et al., 2014** for ref.). Several genes associated with SCZ have undergone positive selection following the human brain evolution (**Xu et al., 2015**). Despite the global network properties of the brain transcriptome are highly conserved among the species there are robust human-specific

disease-associated modules (**Miller et al., 2010**) and human accelerated regions (HARs) - highly conserved parts of genome that underwent accelerated evolution in humans (**Pollard et al., 2006**). HARs can serve as genomic markers for human-specific traits underlying a recent acquisition of modern human cognitive abilities by brain (**Boyd et al., 2015**) but that also "might have led to an increase in structural instability… resulted in a higher risk for neurodegeneration in the aging brain" (**Zhou et al., 2015**), rendering our intellectual abilities genetically fragile (**Crabtree, 2013**) and resulting in a variety of CDs. The role genomic context, epistasis (**Hemani et al., 2014**), plays in the evolution and pathology is manifested by frequently found disease-causing alleles present in animals without obvious pathological symptoms for the host (**Jordan et al., 2015**). Any CD is characterized by general intellectual disability (GID) plus psychiatric symptoms. A genetic perturbation-exerted behavioral cognitive deficit (BCD) in an animal model organism is a poor match to a human CD *per se* due to very poor contextual resemblance between the human GID and animal BCD together with the absence of interpretable psychiatric symptoms. No wonder that the compounds that "cure" mice models consistently fail in human trials (discussed in **Hyman, 2014**).

***NTNG* paralogs brain transcriptome intrinsic complementarity and possible mechanism for the IQ-affecting mutation alleles effect.** There is no global change at the mRNA level between healthy subjects and SCZ patients (**Figure 1B**). This conclusion is supported by previously published works stating that globally altered mRNA expression of *NTNG1* or *NTNG2* is unlikely to confer disease susceptibility, at least in the temporal lobe (**Eastwood and Harrison, 2008**), and Brodmann's area (**Aoki-Suzuki et al., 2005**). However, the original paper-source of the STG samples RNA-seq along with many other genes (>1,000) found that *NTNG1* (but not *NTNG2*) falls under the group of genes with significant alternative promoter usage (**Wu et al., 2012**: **ST6**, p<9.05E-10 at FDR <0.5) and *NTNG2* (but not *NTNG1*) clusters with genes (>700) with significant alternative splicing change (**Wu**

et al., 2012: **ST7**, p<6.15E-12 at FDR<0.5) when SCZ and controls are compared. Such GWAS observation adds an extra layer of complementary regulation to both *NTNG* paralogs on a top of the described in the results section complementary usage rule for the exons, formed unspliced splicing modules, resulting transcripts and their comprising exons (**Figure 1B**). Based on the available RNA-seq dataset it was almost impossible to detect RNA with the matched position of *NTNG* SNPs used for the IQ testing (**ST2c**) except for two coding exons located (rs2149171 and rs3824574) and exon 10 non-coding area located but transcribed rs4915045 (in 2 out of 16 samples). This fact points towards indirect effect of the IQ-affecting mutation alleles potentially associated with shorter (secretable) isoforms generation (**Prosselkov et al., unpublished**) lacking two of the most prominent *NTNG* features: GPI-link and the Ukd domain through an aberrant splicing factor binding. The GPI-link is a hallmark of Netrin-G family members (**Nakashiba et al., 2000, 2002**) and without it the aberrant Netrin-G isoforms are likely to mimic the action of their releasable ancestry molecules - netrins, still being able to bind to their cognate postsynaptic ligand – NGL but without forming an axonal-postsynaptic contact. The Ukd domain of Netrin-G1, despite its so-far unknown function, is involved in lateral binding to the pre-synaptically localised LAR modulating the binding strength between NGL-1 and Netrin-G1 (**Song et al., 2013**). Work is currently underway in search for a similar lateral interaction partner for the Netrin-G2 Ukd domain (**Kim E, personal communications, April 2014**). The inclusion of Ukd encoding exons 6 and 7 is regulated by the Nova splicing factor (**Ule et al., 2005**) affecting the cortex Netrin-G1 exon 7 but not exon 6, and, simultaneously, Netrin-G2 paralog exons exhibiting an opposite pattern. In general, it is tempting to speculate that deregulation of *NTNG* transcripts processing may have a role in the brain-controlled cognitive abilities and associated CDs. Supporting such notion, a decreased level of Netrin-G1c mRNA (exons 6-9 excluded, **Figure 1B-1**) has been reported for BD and SCZ (**Eastwood and Harrison, 2008**) with Netrin-G1d

(exons 6 and 7 included but 8-9 excluded, **Figure 1B-1**) and Netrin-G1f (a secretable short isoform consisted of domain VI only and lacking the Ukd and GPI-link) being increased in BD, but not in SCZ, in anterior cingulated cortex (**Eastwood and Harrison, 2010**). Higher Netrin-G1d mRNA expression in fetal brain but low for the Netrin-G1c isoform in the human adult (**Eastwood and Harrison, 2008**) indicates different functionality of these two splice variants joggling with the Ukd domain inclusion. And, according to our other data, if Netrin-G1 Ukd-containing isoforms are the dominant isoforms in adult mouse brain, Netrin-G2 Ukd-containing isoforms are present only at the trace level (**Prosselkov et al., forthcoming**), resembling a similar transcriptome pattern for the human STG samples (**Figure 1B-1** and **B-2**). A similar "dynamic microexon regulation" associated with the protein interactome misregulation has been reported to be linked to ASD (**Irimia et al., 2014**).

Synchronous and complementary expression of *NTNG* paralogs in the human brain supports the IQ-associated cognitive endophenotypes. Influential parieto-frontal integration theory (P-FIT, **Jung and Haier, 2007**) states that general intelligence ("g") is dependent on multiple brain cortical areas such as dlPFC, Broca's and Wernicke's areas, somatosensory and visual cortices (**Colom et al., 2009**). Despite "g" is widely accepted as the only correlate of the intelligence, its unitary nature was challenged by (**Hampshire et al., 2012)** claiming had indentified two independent brain networks (for memory and for reasoning) responsible for the task performance, the idea later criticised for the employed data processing approach (**Haier et al., 2014**). Higher IQ scores (a composite surrogate of "g") have been reportedly associated with the fronto-parietal network (FPN) connectivity (**Song et al., 2008**; **Glascher et al., 2009**). High level of *NTNG* paralogs expression within the cognition intensively loaded areas of the brain and the distinct patterns of expression profiles (synchronous, asynchronous/mixed, and complementary, **Figure 2A**) support associations of *NTNG1* and *NTNG2* with the recorded cognitive endophenotypes (**Prosselkov**

et al., 2015). Based on the expression patterning over the human life-span, among the total 16 analysed brain areas we found two falling under the same "anti-phasic (complementary)" classifier (**Figure 2C**): HIP and MD. Adding more to that, MD is the only brain area (out of the 16 presented) where *NTNG1* expression level exceeds that of *NTNG2* making it a promising candidate for the phenomena of *NTNGs* SF explanation. Two other brain areas classified by a synchronous paralogs expression deserve a special attention, dlPFC and mPFC (**Figure 2A-4**). PFC circuitry has been known as a "hub of the brain's WM system" (**Kim et al., 2013; Markowitz et al., 2015**), which acts through direct HIP afferents (**Spellman et al., 2015**) and has many connections with other cortical and subcortical areas (**Riga et al., 2014**). mPFC may function as an intelligence-control switchboard and lPFC, part of the FPN global connectivity, predicts the WM performance and fluid intelligence (**Cole et al., 2012**). Interactions of the auditory recognition information fed by the vPFC stream with the sequence processing by the dorsal stream are crucial for the human language articulation (**Skeide and Friederici, 2015; Thothathiri and Rattinger, 2015**). The fact that both *NTNG* paralogs are extensively expressed across PFC (**Figure 2A-2 and A-4**) pinpoints this area as a key for future molecular studies of the human-unique symbolic communications. And PFC is not only implicated in many psychiatric disorders, including SCZ (**Gulsuner and McClellan, 2014**; see also **Riga et al., 2014** for ref.), but is also the only brain structure unique to primates without known homologs in the animal kingdom (**Wise, 2008**).

Evolution of the protein paralogs encoded by the *NTNGs*. Forkhead box P2 (FOXP2) – a ubiquitously expressed transcription factor that has been reported to be linked to the evolution of human language through T303N, N325S substitutions when compared to a primate ortholog (**Enard et al., 2002**) and is 100% identical to Nea protein (**Krause et al., 2007**). FOXP2 regulates the expression of multiple genes and among them is *LRRC4C* (gene encoding NGL-1 – a post-synaptic target of Netrin-G1) in human and chimpanzee (**Konopka**

305 **et al., 2009**). Netrin-G1 similarly to FOXP2 is a 100% conserved protein among the
306 hominins with only 1 mutation found in chimpanzee which is absent in marmoset (and other
307 primates) and mice proteins (**Prosselkov et al., 2015**). On the other hand, extinct hominins'
308 Netrin-G2 relative to modern human contains T346A point mutation (as per current version
309 of hg19), also found in primates and mouse and known as rs4962173 (dbSNP missense
310 mutation) representing an ancient substitution from Neandethal genomes found in modern
311 humans and reflecting a recent acquisition of the novel allele around 5,300 yrs BC. Nothing
312 is known regarding the functional significance of this mutation but biochemically a
313 substitution of alanine (A) on a polar threonine (T) could bring an extra point of regulation,
314 e.g. a phosphorylation or glycosylation (NetPhos2.0 (**Blom et al., 1999**) assigns a low score
315 for the T346 to be phosphorylated but NetOGlyc4.0 (**Steentoft et al., 2013**) robustly predicts
316 it to be glycosylated, **SM**). Another mutation S371A/V reflects a selective sweep in Netrin-
317 G2 protein from primates to hominins within a similar to T346A functional context when a
318 hydrophobic alanine (in chimpanzee, A)/valine (in marmoset, V) is replaced by a polar serine
319 (S) and a strong positive predictions for glycosylation but not phosphorylation (**SM**). This
320 poses a question whether these two human-specific protein substitutions associate with
321 advanced cognitive traits as they may represent a hidden layer of poorly studied so far protein
322 glycosylation-associated regulatome known to affect the brain function and diseases
323 (**Baenziger, 2012**; **Baenziger, 2013**). Adding more to this, T346 is nested on exon 5 just 20
324 nu away from the affecting WM score rs2274855 (**Prosselkov et al., 2015**), and, together
325 with S371A/V, they are both located within the lowest percent identity area (exons (5-7)) of
326 Netrin-Gs (**Figure 3C**) and, proposedly, contributing to the *NTNG* duplicates SF. There are at
327 least three more protein parts potentially contributing to the gene paralogs specialised
328 function subdivision (based on the low identity scores, **Figure 3C**): the secretory peptide, the
329 GPI-link, and the outmost structurally elaborated unstructured loops (I-III) responsible for the

330 reciprocal binding of Netrin-Gs to their post-synaptic cognate partners, NGL-1 or NGL-2,
331 both containing a C-terminal PDZ-binding domain (**Kim et al., 2006**). An interesting finding
332 was reported in (**Arbuckle et al., 2010**) found a presence of SH3(PSD95) domain binding
333 site (required for the phosphatidylinositol-3-kinase recruitment) in mice Netrin-G2 (100%
334 identical to human) but not in Netrin-G1. The detected SH3 binding site overlaps with the
335 Netrin-G2-loop III responsible for the binding specificity to NGL-2 (**Seiradake et al., 2011;**
336 **Soto et al., 2013; DeNardo et al., 2012**). A plausible working hypothesis would be that
337 while internalised (and being GPI-link naïve/immature) the pre-synaptic Netrin-G2 is bound
338 to SH3-PSD95 via loop III but as soon as being secreted extracellularly (and being attached
339 to the membrane) it is bound to post-synaptic NGL-2. Corroborating this, in the absence of
340 Netrin-G2 in the KO mice NGL-2 is unstable on the post-synaptic surface and gets quickly
341 internalized (**Qi et al., in press**). We can only speculate regarding the potential importance of
342 PSD-95(SH3)-Netrin-G2-NGL-2 scaffolding loop interaction/competition but the ability for
343 Netrin-G1 to bind to SH3 has not been reported. Following this logic, Netrin-G1 should have
344 a similar binding partner via loop II while internalised.

345 The overall identical structural scaffold among the Netrin-G paralogs (**Figure 3D**) is
346 likely to represent an anciently preserved one of the primordial protein (encoded by a single
347 gene in the primitive urochordate *C.intestinalis*) and its contribution to the process of SF
348 among the *NTNG* paralogs goes against the "structure drives function" concept. It looks like
349 that it is not the "structure" but rather the "evolution" itself that drives a selection for the best
350 structural (or unstructural in our case) fit out of the available frameworks provided by the
351 gene duplicates to fulfill the emerged functional demand in a new ecological niche. The
352 intricate variability of phenotype is grounded by the conserved nature of genotype and
353 constrained by the "structure-function" limitations of the coding DNA and is only possible
354 due to permissive evolutionary continuing elaborations of non-coding areas able to absorb the

most recently acquired elements (having a potential to become regulatory at some point, e.g. like HAR5 (**Boyd et al., 2015**)) and carried over by neutral drift as proposed by Kimura but for proteins (**Kimura, 1983**). At the same time, the multiple protein substitutions coinciding with the SF labor segregation phenomena among the Netrin-G paralogs question their neutral nature. Both of them undergo a purifying selection from mice to human through the reduction in size of non-coding DNA (introns) and encoded proteins (the mice Netrin-G2 is 2 aa longer its human ortholog) further contributing to the host-specific SF. Thus while the non-coding sequences are used to explore the evolutionary space in time, the restrictive boundaries of the paralogs SF are determined by the protein (unstructured) elements.

Molecular evolution of the Cognitive Complement (CC). Appearance of the neural crest (**Abitua et al., 2012**), an event that "affected the chordate evolution in the unprecedented manner" (**Green et al., 2015**), multipotent progenitor cells (**Stolfi et al., 2015**), and neurogenic placodes (suggesting a chemosensory and neurosecretory activities, **Abitua et al., 2015**) in first primitive urochordates/tunicates coincides with the presence of *Ntng* precursor gene (ENSCING00000024925) later undergoing two rounds of duplication events in lamprey and found to affect human cognitive abilities (**Prosselkov et al., 2015**). *NTNG* paralogs are expressed in the human neural crest-forming cells with *NTNG2* 10 times stronger than *NTNG1* (**Rada-Iglesias et al., 2012**), both are differentially expressed in human comparing to chimpanzee and rhesus monkey with *NTNG2* expression model showing stronger probability than *NTNG1* (**Iskow et al., 2012**), and both are stronger expressed in human telencephalon comparing to chimpanzee and macaque (**Konopka et al., 2012**). *NTNG1* has been classified as a brain module hub gene "whose pattern fundamentally shifted between species" (**Hawrylycs et al., 2015**). Belonging to distinct modules of brain expression regulation (**Liu et al., 2012**, **Konopka et al., 2012**), *NTNGs* are classified as "genes with human-specific expression profiles" (**Liu et al., 2012**). The nearby gene ~260 kbp upstream of *NTNG2* is

380 *MED27* (mediator of RNA polymerase II) has been proposed to be associated with the
381 evolution of human-specific traits (**McLean et al., 2011**). *NTNG1* has also been reported
382 among the "adaptive plasticity genes" (**Ghalambor et al., 2015**) potentiating rapid adaptive
383 evolution in guppies (*NTNG2* was not found among the input RNA for analysis).

384 Complementarity among the *NTNG* paralogs and encoded by them proteins has been
385 reported previously: brain expression complementary pattern (in almost self-exclusive
386 manner) defined by the 5'-UTR-localised *cis*-regulatory elements (**Yaguchi et al., 2014**);
387 complementary distribution within the hippocampal laminar structures (**Nishimura-Akiyoshi**
388 **et al., 2007**); axon-dendrite synaptic ending resulting in differential control over the neuronal
389 circuit plasticity (**Matsukawa et al., 2014**); mutually-exclusive binding pattern to post-
390 synaptic partners, NGL-1 and NGL-2, dictated by the protein unstructural elements
391 (**Seiradake et al., 2011**); alternative promoter usage *vs* alternative mRNA splicing (**Wu et al.,**
392 **2012**) and increased coefficient of variation (CV, **ST1d**) for *NTNG1* expression but not
393 *NTNG2* in SCZ patients (similar to **Zhang et al., 2015**); KO mice behavioral phenotypes and
394 subcellular signaling partners complementarity (**Qi et al., in press**); "differential stability"
395 brain modules expression (*NTNG1* is expressed in the dorsal thalamus (M11) as a hub gene
396 (Pearson's 0.92) while *NTNG2* is in neocortex and claustrum module (M6, Pearson's 0.65))
397 (**Hawrylycs et al., 2015**); hypocretin neurons-specific expression of *NTNG1* (but not
398 *NTNG2*) as a sleep modulator (**Yelin-Bekerman et al., 2015**); top-down *vs* bottom-up
399 information flows gating in mice and differential responsiveness to neuronal stimuli
400 (**Prosselkov et al., forthcoming**); and human IQ-compiling cognitive domains
401 complementation (**Prosselkov et al., 2015**). The current study reports the *NTNGs*
402 complementarity association with the CDs (**Figure 1A**); mRNA splicing pattern
403 complementary at the quantitative and qualitative levels via differential use of the middle-
404 located exons (**Figure 1B**); brain complementary oscillatory expression over the human life

405 span observed in the intensive cognitively loaded brain areas (**Figure 2**); AE of the paralogs-
406 segregated unique non-coding elements (**Figure 3A**); complementary pattern of the protein
407 orthologs (mice-to-human) protein sequence evolution. Such multi-level complementation is
408 likely to reflect a shared evolutionary origin from a single gene in a primitive vertebrate
409 organism 700 mln yrs ago and its subsequent functional segregation among the evolution-
410 generated gene duplicates in jawless fish, such as lamprey.

411 Occupying independent but intercalating functional niches, *NTNG1* and *NTNG2* do
412 not compensate but complement each other's function forming a "functional complement" of
413 genes. Half a billion yrs ago the doubled gene dosage led to the gradual SF and manifested in
414 a function complementation within the cognitive domains, at least in human. We would like
415 to coin such gene pair as a Cognitive Complement (CC).

416

417 CONCLUSION

418 The emerged functional redundancy, as an outcome of gene duplication, leads to function
419 subdivision and its bifurcation among the gene paralogs resulting in the paralogs SF. A
420 functional compensation is known to exist among the evolutionary unrelated genes but has
421 not been reported among the gene paralogs, more frequently characterized by the function
422 complementation. Gene paralogs structural identity (at both, gene and protein levels) does not
423 provide a substrate for functional compensation but rather for complementation, perturbating
424 "structure drives function" rule. A gene duplication event of a tunicate *NTNG* primordial
425 gene and the subsequent process of its function specialisation (driven by the new ecological
426 niches appearance and evolution) among the gene duplicates made them to SF into distinct
427 cognitive domains in a complementary manner forming a CC. In our forthcoming work we
428 are to describe how *Ntng* mice genes function resembles that of human orthologs (**Prosselkov**
429 **et al., forthcoming**).

430

MATERIALS AND METHODS

Human brain *NTNG* transcriptome reconstruction. Relates to **Figure 1B** and **1-C**. The original source of the dataset was produced by (**Wu et al., 2012**: E-MATB-1030) and the downloaded .bam files used for the re-processing are listed in **ST1a**. All reconstructed transcripts are presented in **ST1d** standalone Excel file. Two samples were excluded from the analysis due to failed "per base sequence quality" measure, and zero expression level for *NTNG1a* and *NTNG1int(9-10)* otherwise consistently expressed throughout other samples (**ST1b**). SAMtools software was used for the SNPs calling from the available RNA-seq datasets (**ST1c**). For details refer to **SM**.

Human brain expression profiling for *NTNGs* across the life span. The original source of data was www.brainspan.org. All available samples were initially included into the analysis but two of them excluded at a later stage (MD for 12-13 pcw and mPFC for 16-19 pcw) due to high deviation (6-7 times) from the mean for other replicas. The mean expression values per each brain area as RPKM were plotted against the sampling age. Profiles classification was done visually considering the trend over the all plotted points as an average.

***NTNG1* (*NTNG1m*) and *NTNG2* (*NTNG2b*) full-length mRNA transcripts assembly.** Relates to **Figure 3B.** Human *NTNG1m* brain transcript has been reported previously (**Meerabux et al., 2005**) and we have also confirmed its ortholog presence in the mice brain via full-length cloning (**Prosselkov et al., unpublished**). Since NCBI contains only its partial CDS (AY764265), we used the RNA-seq-generated exons (**Figure 1B**) to reconstruct its full-length and to generate an ORF of the encoded Netrin-G1m. Similarly, human *NTNG2b* was reconstructed from the RNA-seq dataset and from Ensemble as follows. Exon 5 sequence was deduced from ENST00000372179, other exons were from ENST00000467453 (no longer available on the current version of Ensemble) except for exon 6 deduced by running three independent alignments against the human genomic DNA with the mice 3'-intron (5-6),

455 exon 6, and 5'-intron (6-7) concomitantly confirmed by the generated full-length ORF for
456 Netrin-G2b. The reconstructed protein was predicted to encode 587 amino acids, which is in
457 a close proximity to the mice netrin-G2b ortholog of 589 residues (**Prosselkov et al., forth.**).
458 **Full-lengths gene structures of *NTNG* paralogs reconstruction.** Relates to **Figure 3A.**
459 Both, the obtained above from the STG brain samples RNA-seq and the reconstructed full-
460 lengths transcripts carrying all stably expressed exons were used to confirm the intron-exon
461 junctions positioning for *NTNG1* and *NTNG2*. Due to observed variability in the intron (1-2)
462 and exon 10 sizes their boundaries were left unmarked.
463
464 SUPPLEMENTARY MATERIALS (**SM**)
465 Contain Supplementary Methods (RNA-seq of STG re-processing and SNPs detection) and
466 Supplementary Tables (**ST1a-d, ST2**) as a single compiled pdf file. Reconstructed RNA-seq
467 (.gtf) of the STG is presented as a standalone Excel file (**ST1d**). Also included: Netrin-G2b
468 predicted phosphorylation and *O*-glycosylation, Netrin-G1 *vs* Netrin-G2 Ukd alignment
469 (**McWilliam et al., 2013)**, predicted secretory peptide cleavage and GPI attachments.
470
471 ACKNOWLEDGEMENTS
472 This work was in part supported by the "Funding Program for World-Leading Innovative
473 R&D on Science and Technology (FIRST Program)" initiated by the Council for Science and
474 Technology Policy (CSTP), and KAKENHI 15H04290 from the Japan Society for the
475 Promotion of Science (JSPS).
476
477 COMPETING INTERESTS
478 Authors would like to express a lack of any competing interests associated with the work.
479

479 REFERENCES

480 **Abitua PB**, Wagner E, Navarrete IA, Levine M. 2012. Identification of a rudimentary neural
481 crest in a non-vertebrate chordate. *Nature* **492:**104-107. doi: 10.1038/nature11589.

482 **Abitua PB**, Gainous TB, Kaczmarczyk AN, Winchell CJ, Hudson C, Kamata K, Nakagawa
483 M, Tsuda M, Kusakabe, TG, Levine M. 2015. The pre-vertebrate origins of neurogenic
484 placodes. *Nature* **524:**462-465. doi: 10.1038/nature14657.

485 **Akula N**, Barb, J, Jiang, X, Wendland, JR, Choi, KH, Sen, SK, Hou, L, Chen, DTW, Laje, G,
486 Johnson, K, Lipska, BK, Kleinman, JE, Corrada-Bravo, H, Detera-Wadleigh, S, Munson,
487 PJ, McMahon, FJ. 2014. RNA-sequencing of the brain transcriptome implicates
488 dysregulation of neuroplasticity, circadian rhythms and GTPase binding in bipolar
489 disorder. *Molecular Psychiatry* **19:**1179-1185. doi: 10.1038/mp.2013.170.

490 **Aoki-Suzuki M**, Yamada K, Meerabux J, Iwayama-Shigeno Y, Ohba H, Iwamoto K, Takao
491 H, Toyota T, Suto Y, Nakatani N, Dean B, Nishimura S, Seki K, Kato T, Itohara S,
492 Nishikawa T, Yoshikawa, T. 2005. A Family-Based Association Study and Gene
493 Expression Analyses of Netrin-G1 and -G2 Genes in Schizophrenia. *Biological Psychiatry*
494 **57:**382–393. doi: 10.1016/j.biopsych.2004.11.022.

495 **Arbuckle MI**, Komiyama NH, Delaney A, Coba M, Garry EM, Rosie R, Allchorne AJ,
496 Forsyth LH, Bence M, Carlisle HJ, O'Dell TJ, Mitchell R, Fleetwood-Walker SM, Grant
497 SGN. 2010. The SH3 domain of postsynaptic density 95 mediates inflammatory pain
498 through phosphatidylinositol-3-kinase recruitment. *Embo Reports* **11:**473-478. doi:
499 10.1038/embor.2010.63.

500 **Archer HL**, Evans JC, Millar DS, Thompson PW, Kerr AM, Leonard H, Christodoulou J,
501 Ravine D, Lazarou L, Grove L, Verity C, Whatley SD, Pitz DT, Sampson JR, Clarke AJ.
502 2006. *NTNG1* mutations are a rare cause of Rett syndrome. *American Journal of Medical*
503 *Genetics Part A* **140A:**691-694. doi: 10.1002/ajmg.a.31133.

504 **Ayalew M,** Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD, Winiger E, Breier A,
505 Shekhar A, Amdur R, Koller D, Nurnberger JI, Corvin A, Geyer M, Tsuang MT, Salomon
506 D, Schork NJ, Fanous AH, O'Donovan MC, Niculescu AB. 2012. Convergent functional
507 genomics of schizophrenia: from comprehensive understanding to genetic risk prediction.
508 *Molecular Psychiatry* **17:**887-905. doi: 10.1038/mp.2012.37.

509 **Baenziger JU.** 2012. Moving the *O*-glycoproteome from form to function. *Proceedings of*
510 *the National Academy of Sciences of the United States of America* **109:**9672–9673. doi:
511 10.1073/pnas.1206735109.

512 **Baenziger JU.** 2013. *O*-mannosylation of cadherins. *Proceedings of the National Academy of*
513 *Sciences of the United States of America* **110:**20858-20859. doi:
514 10.1073/pnas.1321827111.

515 **Bisgaard A-M,** Rasmussen LN, Moller HU, Kirchhoff M, Bryndorf T. 2007. Interstitial
516 deletion of the short arm of chromosome 1 (1p13.1p21.1) in a girl with mental retardation,
517 short stature and colobomata. *Clinical Dysmorphology* **16:**109-112. doi:
518 10.1097/01.mcd.0000228425.89660.bf.

519 **Blom N,** Gammeltoft S, Brunak S. 1999. Sequence and structure-based prediction of
520 eukaryotic protein phosphorylation sites. *Journal of Molecular Biology* **294:**1351-1362.
521 doi: 10.1006/jmbi.1999.3310.

522 **Boraska V,** Franklin CS, Floyd JAB, Thornton LM, Huckins LM, Southam L, Rayner NW,
523 Tachmazidou I, Klump KL, Treasure J, Lewis CM, Schmidt U, Tozzi F, Kiezebrink K,
524 Hebebrand J, Gorwood P, Adan RAH, Kas MJH, Favaro A, Santonastaso P, Fernández-
525 Aranda F, Gratacos M, Rybakowsk F, Dmitrzak-Weglarz M, Kaprio J, Keski-RahkonenA,
526 Raevuori A, Van Furth EF, Slof-Op 't Landt MCT, Hudson JI, Reichborn-Kjennerud T,
527 Knudsen GPS, Monteleone P, Kaplan AS, Karwautz A, Hakonarson H, Berrettini WH,
528 Guo Y, Li D, Schork NJ, Komaki G, Ando T, Inoko H, Esko T, Fischer K, Männik K,

529 Metspalu A, Baker JH, Cone RD, Dackor J, DeSocio JE, Hilliard CE, O'Toole JK, Pantel
530 J, Szatkiewicz JP, Taico C, Zerwas S, Trace SE, Davis OSP, Helder S, Bühren K,
531 Burghardt R, de Zwaan M, Egberts K, Ehrlich S, Herpertz-Dahlmann B, Herzog W,
532 Imgart H, Scherag A, Scherag S, Zipfel S, Boni C, Ramoz N, Versini A, Brandys MK,
533 Danner UN, de Kovel C, Hendriks J, Koeleman BPC, Ophoff RA, Strengman E, van
534 Elburg AA, Bruson A, Clementi M, Degortes D, Forzan M, Tenconi E, Docampo E,
535 Escaramís G, Jiménez-Murcia S, Lissowska J, Rajewski A, Szeszenia-Dabrowska N,
536 Slopien A, Hauser J, Karhunen L, Meulenbelt I, Slagboom PE, Tortorella A, Maj M,
537 Dedoussis G, Dikeos D, Gonidakis F, Tziouvas K, Tsitsika A, Papezova H, Slachtova L,
538 Martaskova D, Kennedy JL, Levitan RD, Yilmaz Z, Huemer J, Koubek D, Merl E,
539 Wagner G, Lichtenstein P, Breen G, Cohen-Woods S, Farmer A, McGuffin P, Cichon S,
540 Giegling I, Herms S, Rujescu D, Schreiber S, Wichmann H-E, Dina C, Sladek R,
541 Gambaro G, Soranzo N, Julia A, Marsal S, Rabionet R, Gaborieau V, Dick DM, Palotie A,
542 Ripatti S, Widén E, Andreassen OA, Espeseth T, Lundervold A, Reinvang I, Steen VM,
543 Le Hellard S, Mattingsdal M, Ntalla I, Bencko V, Foretova L, Janout V, Navratilova M,
544 Gallinger S, Pinto D, Scherer SW, Aschauer H, Carlberg L, Schosser A, Alfredsson L,
545 Ding B, Klareskog L, Padyukov L, Courtet P, Guillaume S, Jaussent I, Finan C, Kalsi G,
546 Roberts M, Logan DW, Peltonen L, Ritchie GRS, Barrett JC, The Wellcome Trust Case
547 Control Consortium 3, Estivill X, Hinney A, Sullivan PF, Collier DA, Zeggini E, Bulik
548 CM. 2014. A genome-wide association study of anorexia nervosa. *Molecular Psychiatry*
549 **19:**1084-1094. doi: 1085–1094. 10.1038/mp.2013.187.

550 **Borg I**, Freude K, Kubart SK, Hoffmann K, Menzel C, Laccone F, Firth H, Ferguson-Smith
551 MA, Tommerup N, Ropers HH, Sargan D, Kalscheuer VM. 2005. Disruption of Netrin G1
552 by a balanced chromosome translocation in a girl with Rett syndrome. *European Journal*
553 *of Human Genetics* **13:**921-927. doi: 10.1038/sj.ejhg.5201429.

554 **Boyd JL,** Skove SL, Rouanet JP, Pilaz L-J, Bepler T, Gordân R, Wray GA, Silver DL. 2015.
555 Human-Chimpanzee Differences in a FZD8 Enhancer Alter Cell-Cycle Dynamics in the
556 Developing Neocortex. *Current Biology* **25:**772-779. doi: 10.1016/j.cub.2015.01.041.
557 **Cavard C**, Audebourg A, Letourneur F, Audard V, Beuvon F, Cagnard N, Radenen, B,
558 Varlet P, Vacher-Lavenu M-C, Perret C, Terris B. 2009. Gene expression profiling
559 provides insights into the pathways involved in solid pseudopapillary neoplasm of the
560 pancreas. *Journal of Pathology* **218:**201-209. doi: 10.1002/path.2524.
561 **Cole MW**, Yarkoni T, Repovs G, Anticevic A, Braver TS. 2012. Global Connectivity of
562 Prefrontal Cortex Predicts Cognitive Control and Intelligence. *Journal of Neuroscience*
563 **32:**8988-8999. doi: 10.1523/jneurosci.0536-12.2012.
564 **Colom R,** Haier RJ, Head K, Álvarez-Linerac J, Ángeles Quiroga M, Shih PC, Jung RE.
565 2009. Gray matter correlates of fluid, crystallized, and spatial intelligence: Testing the P-
566 FIT model. *Intelligence* **37:**124-135. doi: 10.1016/j.intell. 2008.07.007.
567 **Crabtree GR.** 2013. Our fragile intellect. Part I. *Trends in Genetics* **29:**1-3. doi:
568 10.1016/j.tig.2012.10.002.
569 **DeNardo LA,** de Wit J, Otto-Hitt S, Ghosh A. 2012. NGL-2 Regulates Input-Specific
570 Synapse Development in CA1 Pyramidal Neurons. *Neuron* **76:**762-775. doi:
571 10.1016/j.neuron.2012.10.013.
572 **D'Gama AM,** Pochareddy S, Li M, Jamuar SS, Reiff RE, Lam A-TN, Sestan N, Walsh CA.
573 2015. Targeted DNA Sequencing from Autism Spectrum Disorder Brains Implicates
574 Multiple Genetic Mechanisms. *Neuron* **88:**910-917. doi: 10.1016/j.neuron.2015.11.009.
575 **Eastwood SL,** Harrison PJ. 2008. Decreased mRNA expression of netrin-G1 and netrin-G2
576 in the temporal lobe in schizophrenia and bipolar disorder. *Neuropsychopharmacology*
577 **33:**933-945. doi: 10.1038/sj.npp.1301457.
578 **Eastwood SL,** Harrison PJ. 2010. Markers of Glutamate Synaptic Transmission and

579 Plasticity Are Increased in the Anterior Cingulate Cortex in Bipolar Disorder. *Biological*
580 *Psychiatry* **67:**1010-1016. doi: 10.1016/j.biopsych.2009.12.004.

581 **Eaton WW,** Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, Mortensen PB. 2006.
582 Association of schizophrenia and autoimmune diseases: Linkage of Danish National
583 Registers. *American Journal of Psychiatry* **163:**521-528. doi: 10.1176/appi.ajp.163.3.521.

584 **Eisenhaber B,** Bork P, Yuan YP, Loffler G, Eisenhaber F. 2000. Automated annotation of
585 GPI anchor sites: case study *C. elegans. Trends in Biochemical Sciences* **25:**340-341. doi:
586 10.1016/s0968-0004(00)01601-7.

587 **Enard W,** Przeworski M, Fisher SE, Lai CSL, Wiebe V, Kitano T, Monaco AP, Pääbo S.
588 2002. Molecular evolution of *FOXP2*, a gene involved in speech and language. *Nature*
589 **418:**869-872. doi: 10.1038/nature01025.

590 **Finn ES,** Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X,
591 Constable RT. 2015. Functional connectome fingerprinting: identifying individuals using
592 patterns of brain connectivity. *Nature Neuroscience* **online.** doi:10.1038/nn.4135.

593 **Forbes NF,** Carrick LA, McIntosh AM, Lawrie SM. 2009. Working memory in
594 schizophrenia: a meta-analysis. *Psychological Medicine* **39:**889-905. doi:
595 10.1017/s0033291708004558.

596 **Fukasawa M,** Aoki M, Yamada K, Iwayama-Shigeno Y, Takao H, Meerabux J, Toyota T,
597 Nishikawa T, Yoshikawa T. 2004. Case-control association study of human netrin G1
598 gene in Japanese schizophrenia. *Journal of Medical and Dental Sciences* **51:** 121-128.

599 **Ghalambor CK,** Hoke KL, Ruell EW, Fischer EK, Reznick DN, Hughes KA. 2015. Non-
600 adaptive plasticity potentiates rapid adaptive evolution of gene expression in nature.
601 *Nature* **525:**372-375. doi: 10.1038/nature15256.

602 **Gilissen C,** Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BWM, Willemsen MH,
603 Kwint M, Janssen IM, Hoischen A, Schenck A, Leach R, Klein R, Tearle R, Bo T, Pfundt

604 R, Yntema HG, de Vries BBA, Kleefstra T, Brunner HG, Vissers LELM, Veltman JA.
605 2014. Genome sequencing identifies major causes of severe intellectual disability. *Nature*
606 **511:**344-347. doi: 10.1038/nature13394.
607 **Glascher J,** Tranel D, Paul LK, Rudrauf D, Rorden C, Hornaday A, Grabowski T, Damasio
608 H, Adolphs R. 2009. Lesion Mapping of Cognitive Abilities Linked to Intelligence.
609 *Neuron* **61:**681-691. doi: 10.1016/j.neuron.2009.01.026.
610 **Green SA,** Simoes-Costa M, Bronner ME. 2015. Evolution of vertebrates as viewed from the
611 crest. *Nature* **520:**474-482. doi: 10.1038/nature14436.
612 **Guilloux JP,** Gaiteri C, Sibille E. 2010. Network analysis of positional candidate genes of
613 schizophrenia highlights ... more than ... myelin-related pathways. *Molecular Psychiatry*
614 **15:**786-788. doi: 10.1038/mp.2009.68.
615 **Gulsuner S and McClellan JM.** 2014. *De Novo* Mutations in Schizophrenia Disrupt Genes
616 Co-Expressed in Fetal Prefrontal Cortex. *Neuropsychopharmacology* **39:**238-239. doi:
617 10.1038/npp.2013.219.
618 **Haier RJ,** Karama S, Colom R, Jung R, Johnson W. 2014. A comment on "Fractionating
619 Intelligence" and the peer review process. *Intelligence* **46:**323–332. doi:
620 10.1016./j.intell.2014.02.007.
621 **Hampshire A,** Highfield RR, Parkin BL, Owen AM. 2012. Fractionating Human Intelligence.
622 *Neuron* **76:**1225-1237. doi: 10.1016/j.neuron.2012.06.022.
623 **Hawrylycz M,** Miller JA, Menon V, Feng D, Dolbeare T, Guillozet-Bongaarts AL, Jegga
624 AG, Aronow BJ, Lee C-K, Bernard A, Glasser MF, Dierker DL, Menche J, Szafer A,
625 Collman F, Grange P, Berman KA, Mihalas S, Yao Z, Stewart L, Barabási A-L, Schulkin
626 J, Phillips J, Ng L, Dang C, Haynor DR, Jones A, Van Essen DC, Koch C, Lein E. 2015.
627 Canonical genetic signatures of the adult human brain. *Nature Neuroscience* **18:**1832-
628 1844. doi: 10.1038/nn.4171.

629 **Hemani G,** Shakhbazov K, Westra H-J, Esko T, Henders AK, McRae AF, Yang J, Gibson G,
630 Martin NG, Metspalu A, Franke L, Montgomery GW, Visscher PM, Powell JE. 2014.
631 Detection and replication of epistasis influencing transcription in humans. *Nature*
632 **508**:249–253. doi: 10.1038/nature13005.

633 **Hyman SE.** 2014. How Far Can Mice Carry Autism Research? *Cell* **158:**13-14. doi:
634 10.1016/j.cell.2014.06.032.

635 **Iossifov I,** O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, Stessman HA,
636 Witherspoon KT, Vives L, Patterson KE, Smith JD, Paeper B, Nickerson DA, Dea J,
637 Dong S, Gonzalez LE, Mandell JD, Mane SM, Murtha MT, Sullivan CA, Walker MF,
638 Waqar Z, Wei L, Willsey AJ, Yamrom B, Lee Y, Grabowska E, Dalkic E, Wang Z, Marks
639 S, Andrews P, Leotta A, Kendall J, Hakker I, Rosenbaum J, Ma B, Rodgers L, Troge J,
640 Narzisi G, Seungtai Y, Schatz MC, Kenny Y, McCombie WR, Shendure J, Eichler EE,
641 State MW, Wigler M. 2014. The contribution of *de novo* coding mutations to autism
642 spectrum disorder. *Nature* **515:**216–221. doi: 10.1038/nature13908.

643 **Irimia M,** Weatheritt RJ, Ellis JD, Parikshak NN, Gonatopoulos-Pournatzis T, Babor M,
644 Quesnel-Vallières M, Tapial J, Raj B, O'Hanlon D, Barrios-Rodiles M, Sternberg MJE,
645 Cordes SP, Roth FP, Wrana JL, Geschwind DH, Blencowe BJ. 2014. A Highly Conserved
646 Program of Neuronal Microexons Is Misregulated in Autistic Brains. *Cell* **159:**1511-1523.
647 doi: 10.1016/j.cell.2014.11.035.

648 **Ishigaki S,** Masuda A, Fujioka Y, Iguchi Y, Katsuno M, Shibata A, Urano F, Sobue G, Ohno
649 K. 2012. Position-dependent FUS-RNA interactions regulate alternative splicing events
650 and transcriptions. *Scientific Reports* **2**: A529. doi: 10.1038/srep00529.

651 **Iskow RC,** Gokcumen O, Abyzov A, Malukiewicz J, Zhu Q, Sukumara AT, Pai AA, Mills
652 RE, Habegger L, Cusanovich DA, Rubel MA, Perry GH, Gerstein M, Stone AC, Gilade Y,
653 Lee C. 2012. Regulatory element copy number differences shape primate expression

profiles. *Proceedings of the National Academy of Sciences of the United States of America.* **109***:*12656–12661. doi: 10.1073/pnas.1205199109.

Jordan DM, Frangakis SG, Golzio C, Cassa CA, Kurtzberg J, Task Force for Neonatal Genomics, Davis EE, Sunyaev SR, Katsanis N. 2015. Identification of *cis*-suppression of human disease muattions by comparative genomics. *Nature.* **524:**225-229. doi: 10.1038/nature14497.

Jung RE and Haier RJ. 2007. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: Converging neuroimaging evidence. *Behavioral and Brain Sciences* **30:**135-187. doi: 10.1017/s0140525x07001185.

Kim J, Ghim J-W, Lee JH, Jung MW. 2013. Neural Correlates of Interval Timing in Rodent Prefrontal Cortex. *Journal of Neuroscience* **33:**13834-13847. doi: 10.1523/jneurosci.1443-13.2013.

Kim S, Burette A. Chung HS, Kwon SK, Woo J, Lee HW, Kim K, Kim H, Weinberg RJ, Kim E. 2006. NGL family PSD-95-interacting adhesion molecules regulate excitatory synapse formation. *Nature Neuroscience* **9:**1294-1301. doi: 10.1038/nn1763.

Kimura M. 1983. The neutral theory of molecular evolution. Cambridge University Press.

King IF, Yandava CN, Mabb AM, Hsiao JS, Huang HS, Pearson BL, Calabrese JM, Starmer J, Parker JS, Magnuson T, Chamberlain SJ, Philpot BD, Zylka MJ. 2013. Topoisomerases facilitate transcription of long genes linked to autism. *Nature* **501:**58-62. doi: 10.1038/nature12504.

Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao FY, Peng S, Preuss TM, Wohlschlegel JA, Geschwind DH. 2009. Human-specific transcriptional regulation of CNS development genes by FOXP2. *Nature* **462:**213-217. doi: 10.1038/nature08549.

Konopka G, Friedrich T, Davis-Turak J, Winden K, Oldham MC, Gao F, Chen L, Wang G-Z, Luo R, Preuss TM, Geschwind DH. 2012. Human-Specific Transcriptional Networks in

679 the Brain. *Neuron* **23:**601-617. doi: 10.1016/j.neuron.2012.05.034.

680 **Krause J,** Lalueza-Fox C, Orlando L, Enard W, Green RE, Burbano HA, Hublin J-J, Hänni
681 C, Fortea J, de la Rasilla M, Bertranpetit J, Rosas A, Pääbo S. 2007. The derived *FOXP2*
682 variant of modern humans was shared with neandertals. *Current Biology* **17:**1908-1912.
683 doi: 10.1016/j.cub.2007.10.008.

684 **Lagier-Tourenne C,** Polymenidou M, Hutt KR, Vu AQ, Baughn M, Huelga SC, Clutario
685 KM, Ling S-C, Liang TY, Mazur C, Wancewicz E, Kim AS, Watt A, Freier S, Hicks GG,
686 Donohue JP, Shiue L, Bennett CF, Ravits J, Cleveland DW, Yeo GW. 2012. Divergent
687 roles of ALS-linked proteins FUS/TLS and TDP-43 intersect in processing long pre-
688 mRNAs. *Nature Neuroscience* **15:**1488-1497. doi: doi:10.1038/nn.3230.

689 **Lee SH,** Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A,
690 Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A,
691 Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA,
692 Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A,
693 Bauer M, Bayés M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T,
694 Biederman J, Binder EB, Black DW, Blackwood DHR, Bloss CS, Boehnke M, Boomsma
695 DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney
696 WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M,
697 Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook E
698 H, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro
699 ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F,
700 Djurovic S, Donohoe GJ, Doyle AE, Duan JB, Dudbridge F, Duketis E, Ebstein RP,
701 Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M,
702 Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag C
703 M, Friedl M, Frisén L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind

DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan WH, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kähler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landen M, Långström N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu CY, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PAF, Maestrini E, Magnusson PKE, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Mühleisen TW, Muir WJ, Muller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nöthen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnström K, Reif A, Ribasés M,

729 Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G,
730 Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R,
731 Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ,
732 Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi JX, Shilling PD, Shyn
733 SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJS, St
734 Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS,
735 Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F,
736 Treutlein J, Uhr M, van den Oord EJCG, Van Grootheest G, Van Os J, Vicente AM,
737 Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman
738 MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt
739 SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zöllner S,
740 International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), Devlin B,
741 Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW,
742 Kendler KS, Wray NR. 2013. Genetic relationship between five psychiatric disorders
743 estimated from genome-wide SNPs. *Nature Genetics* **45:**984-994. doi: 10.1038/ng.2711.

744 **Lesnick TG,** Papapetropoulos S, Mash DC, Ffrench-Mullen J, Shehadeh L, de Andrade M,
745 Henley JR, Rocca WA, Ahlskog JE, Maraganore DM. 2007. A genomic pathway
746 approach to a complex disease: Axon guidance and Parkinson disease. *PLoS Genetics*
747 **3:**984-995. doi: 10.1371/journal.pgen.0030098.

748 **Lips ES,** Cornelisse LN, Toonen RF, Min JL, Hultman CM, the International Schizophrenia
749 Consortium, Holmans PA, O'Donovan MC, Purcell SM, Smit AB, Verhage M, Sullivan
750 PF, Visscher PM, Posthuma D. 2012. Functional gene group analysis identifies synaptic
751 gene groups as risk factor for schizophrenia. *Molecular Psychiatry* **17:**996-1006. doi:
752 10.1038/mp.2012.37.

753 **Liu XL,** Somel M, Tang L, Yan Z, Jiang X, Guo S, Yuan Y, He L, Oleksiak A, Zhang Y, Li

754 N, Hu YH, Chen W, Qiu ZL, Pääbo S, Khaitovich P. 2012. Extension of cortical synaptic
755 development distinguishes humans from chimpanzees and macaques. *Genome Research*
756 **22:**611-622. doi: 10.1101/gr.127324.111.

757 **Maier R,** Moser G, Chen G-B, Ripke S, Cross-disorder Working Group of the Psychiatric
758 Genomics Consortium, Coryell W, Potash JB, Scheftner WA, Shi J, Weissman MM,
759 Hultman CM, Landén M, Levinson DF, Kendler KS, Smoller JW, Wray NR, Lee SH.
760 2015. Joint Analysis of Psychiatric Disorders Increases Accuracy of Risk Prediction for
761 Schizophrenia, Bipolar Disorder, and Major Depressive Disorder. *The American Journal*
762 *of Human Genetics* **96:**283-294. doi: 10.1016/j.ajhg.2014.12.006.

763 **Markowitz DA,** Curtis CE, Pesaran B. 2015. Multiple component networks support working
764 memory in prefrontal cortex. *Proceedings of the National Academy of Sciences of the*
765 *United States of America* **112:**11084-11089. doi: 10.1073/pnas.1504172112.

766 **Maurano MT,** Humbert R, Rynes E, Thurman RE, Haugen E, Wang H, Reynolds AP,
767 Sandstrom R, Qu HZ, Brody J, Shafer A, Neri F, Lee K, Kutyavin T, Stehling-Sun S,
768 Johnson AK, Canfield TK, Giste E, Diegel M, Bates D, Hansen RS, Neph S, Sabo PJ,
769 Heimfeld S, Raubitschek A, Ziegler S, Cotsapas C, Sotoodehnia N, Glass I, Sunyaev SR,
770 Kaul R, Stamatoyannopoulos JA. 2012. Systematic Localization of Common Disease-
771 Associated Variation in Regulatory DNA. *Science* **337:**1190-1195. doi:
772 10.1126/science.1222794.

773 **McLean CY,** Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, Indjeian VB, Lim
774 XH, Menke DB, Schaar BT, Wenger AM, Bejerano G, Kingsley DM. 2011. Human-
775 specific loss of regulatory DNA and the evolution of human-specific traits. *Nature*
776 **471:**216-219. doi: 10.1038/nature09774.

777 **McWilliam H,** Li W, Uludag M, Squizzato S, Park YM, Buso N, Cowley AP, Lopez R. 2013.
778 Analysis Tool Web Services from the EMBL-EBI. *Nucleic Acids Research* **41:**597-600.

779 doi: 10.1093/nar/gkt376.

780 **Meerabux JMA,** Ohba H, Fukasawa M, Suto Y, Aoki-Suzuki M, Nakashiba T, Nishimura S,
781 Itohara S, Yoshikawa T. 2005. Human netrin-G1 isoforms show evidence of differential
782 expression. *Genomics* **86:**112–116. doi: 10.1016/j.ygeno.2005.04.004.

783 **Miller JA,** Horvath S, Geschwind DH. 2010. Divergence of human and mouse brain
784 transcriptome highlights Alzheimer disease pathways. *Proceedings of the National*
785 *Academy of Sciences of the United States of America* **107:**12698-12703. doi:
786 10.1073/pnas.0914257107.

787 **Nakashiba T,** Ikeda T, Nishimura S, Tashiro K, Honjo T, Culotti JG, Itohara, S. 2000.
788 Netrin-G1: a Novel Glycosyl Phosphatidylinositol-Linked Mammalian Netrin That Is
789 Functionally Divergent from Classical Netrins. *The Journal of Neuroscience* **20:**6540-
790 6550.

791 **Nakashiba T,** Nishimura S, Ikeda T, Itohara S. 2002. Complementary expression and neurite
792 outgrowth activity of netrin-G subfamily members. *Mechanisms of Development* **111:**47-
793 60. doi: 10.1016/S0925-4773(01)00600-1.

794 **Nakaya T,** Alexiou P, Maragkakis M, Chang A, Mourelatos Z. 2013. FUS regulates genes
795 coding for RNA-binding proteins in neurons by binding to their highly conserved introns.
796 *RNA* **19:**498-509. doi: 10.1261/rna.037804.112.

797 **Nectoux J,** Girard B, Bahi-Buisson N, Prieur F, Afenjar A, Rosas-Vargas H, Chelly J,
798 Bienvenu T. 2007. *Netrin G1* mutations are an uncommon cause of atypical Rett
799 syndrome with or without epilepsy. *Pediatric Neurology* **37:**270-274. doi:
800 10.1016/j.pediatrneurol.2007.06.002.

801 **Parikshak NN,** Gandal MJ, Geschwind DH. 2015. Systems biology and gene networks in
802 neurodevelopmental and neurodegenerative disorders. *Nature Reviews Genetics* **16:**441-
803 458. doi: 10.1038/nrg3934.

804 **Prosselkov P,** Hashimoto R, Polygalov D, Kazutaka O, Zhang Q, McHugh TJ, Takeda M,
805 Itohara S. 2015. Cognitive Endophenotypes of modern and extinct hominins associated
806 with NTNG gene paralogs. doi: http://dx.doi.org/10.1101/034413.
807 **Nishimura-Akiyoshi S,** Niimi K, Nakashiba T, and Itohara S. 2007. Axonal netrin-Gs
808 transneuronally determine lamina-specific subdendritic segments. *Proceedings of the*
809 *National Academy of Sciences of the United States of America* **104:**14801-14806. doi:
810 10.1073/pnas.0706919104.
811 **O'Roak BJ,** Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C,
812 Smith JD, Turner EH, Stanaway IB, Vernot B, Malig M, Baker C, Reilly B, Akey JM,
813 Borenstein E, Rieder MJ, Nickerson DA, Bernier R, Shendure J, Eichler EE. 2012a.
814 Sporadic autism exomes reveal a highly interconnected protein network of *de novo*
815 mutations. *Nature* **485:**246-250. doi: 10.1038/nature10989.
816 **O'Roak BJ,** Vives L, Fu WQ, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A,
817 Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe
818 BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier
819 R, Eichler EE, Shendure J. 2012b. Multiplex Targeted Sequencing Identifies Recurrently
820 Mutated Genes in Autism Spectrum Disorders. *Science* **338:**1619-1622. doi:
821 10.1126/science.1227764.
822 **Ohno S.** 1970. Evolution by Gene Duplication. Springer, New York.
823 **Ohtsuki T,** Horiuchi Y, Koga M, Ishiguro H, Inada T, Iwata N, Ozaki N, Ujike H, Watanabe
824 Y, Someya T, Arinami T. 2008. Association of polymorphisms in the haplotype block
825 spanning the alternatively spliced exons of the *NTNG1* gene at 1p13.3 with schizophrenia
826 in Japanese populations. *Neuroscience Letters* **435:**194-197. doi:
827 10.1016/j.neulet.2008.02.053.
828 **Pamplona GSP,** Neto GSS, Rosset SRE, Rogers BP, Salmon CEG. 2015. Analyzing the

association between functional connectivity of the brain and intellectual performance. *Frontiers in Human Neuroscience* **9:**A61. doi: 10.3389/fnhum.2015.00061.

Pan Y, Fang M, Shen L, Wang L, Lv Y, Xi Z, Chen D, Li C, Wang X. 2010. Abnormal expression of netrin-G2 in temporal lobe epilepsy neurons in humans and a rat model. *Experimental Neurology* **224:**340-346. doi: 10.1016/j.expneurol.2010.04.001.

Petersen TN, Brunak S, von Heijne G, Nielsen H. 2011. SignalP 4.0: discriminating signal peptides from transmembrane regions. *Nature Methods* **8:**785-786. doi: 10.1038/nmeth.1701.

Pollard KS, Salama SR, King B, Kern AD, Dreszer T, Katzman S, Siepel A, Pedersen JS, Bejerano G, Baertsch R, Rosenbloom KR, Kent J, Haussler D. 2006. Forces shaping the fastest evolving regions in the human genome. *PLoS Genetics* **2:**1599-1611. doi: 10.1371/journal.pgen.0020168.

Power RA, Steinberg S, Bjornsdottir G, Rietveld CA, Abdellaoui A, Nivard MM, Johannesson M, Galesloot TE, Hottenga JJ, Willemsen G, Cesarini D, Benjamin DJ, Magnusson PKE, Ullén F, Tiemeier H, Hofman A, van Rooij FJA, Walters GB, Sigurdsson E, Thorgeirsson TE, Ingason A, Helgason A, Kong A, Kiemeney LA, Koellinger P, Boomsma DI, Gudbjartsson D, Stefansson H, Stefansson K. 2015. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. *Nature Neuroscience* **18:**953-955. doi: 10.1038/nn.4040.

Preuss TM. 2012. Human brain evolution: From gene discovery to phenotype discovery. *Proceedings of the National Academy of Sciences of the United States of America* **109:**10709-10716. doi : 10.1073/pnas.1201894109.

Rada-Iglesias A, Bajpai R, Prescott S, Brugmann SA, Swigut T, Wysocka J. 2012. Epigenomic Annotation of Enhancers Predicts Transcriptional Regulators of Human Neural Crest. *Cell Stem Cell* **11:**1-16. doi: 10.1016/j.stem.2012.07.006.

Reddy LF, Lee J, Davis MC, Altshuler L, Glahn DC, Miklowitz DJ, Green MF. 2014. Impulsivity and Risk Taking in Bipolar Disorder and Schizophrenia. *Neuropsychopharmacology* **39:**456-463. doi: 10.1038/npp.2013.218.

Richiardi J, Altmann A, Milazzo A-C, Chang C, Chakravarty MM, Banaschewski T, Barker GJ, Bokde ALW, Bromberg U, Büchel C, Conrod P, Fauth-Bühler M, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Lemaître H, Mann KF, Martinot J-L, Nees F, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Spanagel R, Ströhle A, Schumann G, Hawrylycz M, Poline J-B, Greicius MD, IMAGEN consortium. 2015. Correlated gene expression supports synchronous activity in brain networks. *Science* **348:**1241-1244. doi: 10.1126/science.1255905.

Riga D, Matos MR, Glas A, Smit AB, Spijker S, Van den Oever MC. 2014. Optogenetic dissection of medial prefrontal cortex circuitry. *Frontiers in Systems Neuroscience* **8**:A230. doi: 10.3389/fnsys.2014.00230.

Rogelj B, Easton LE, Bogu GK, Stanton LW, Rot G, Curk T, Zupan B, Sugimoto Y, Modic M, Haberman N, Tollervey J, Fujii R, Takumi T, Shaw CE, Ule J. 2012. Widespread binding of FUS along nascent RNA regulates alternative splicing in the brain. *Scientific Reports* **2**:A603. doi: 10.1038/srep00603.

Romero E, Ali C, Molina-Holgado E, Castellano B, Guaza C, Borrell J. 2007. Neurobehavioral and immunological consequences of prenatal immune activation in rats. Influence of antipsychotics. *Neuropsychopharmacology* **32:**1791-1804. doi: 10.1038/sj.npp.1301292.

Scharf JM, Yu D, Mathews CA, Neale BM, Stewart SE, Fagerness JA, Evans P, Gamazon E, Edlund CK, Service SK, Tikhomirov A, Osiecki L, Illmann C, Pluzhnikov A, Konkashbaev A, Davis LK, Han B, Crane J, Moorjani P, Crenshaw AT, Parkin MA, Reus VI, Lowe TL, Rangel-Lugo M, Chouinard S, Dion Y, Girard S, Cath DC, Smit JH, King

879 RA, Fernandez TV, Leckman JF, Kidd KK, Kidd JR, Pakstis AJ, State MW, Herrera LD,
880 Romero R, Fournier E, Sandor P, Barr CL, Phan N, Gross-Tsur V, Benarroch F, Pollak Y,
881 Budman CL, Bruun RD, Erenberg G, Naarden AL, Lee PC, Weiss N, Kremeyer B, Berrío
882 GB, Campbell DD, Silgado JCC, Ochoa WC, Restrepo SCM, Muller H, Duarte AVV,
883 Lyon GJ, Leppert M, Morgan J, Weiss R, Grados MA, Anderson K, Davarya S, Singer H,
884 Walkup J, Jankovic J, Tischfield JA, Heiman GA, Gilbert DL, Hoekstra PJ, Robertson
885 MM, Kurlan R, Liu C, Gibbs JR, Singleton A for the North American Brain Expression
886 Consorium, Hardy J for the UK Human Brain Expression Database, Strengman E, Ophoff
887 RA, Wagner M, Moessner R, Mirel DB, Posthuma D, Sabatti C, Eskin E, Conti DV,
888 Knowles JA, Ruiz-Linares A, Rouleau GA, Purcell S, Heutink P, Oostra BA, McMahon
889 WM, Freimer NB, Cox NJ, Pauls DL. 2013. Genome-wide association study of Tourette's
890 syndrome. *Molecular Psychiatry* **18:**721-728. doi: 10.1038/mp.2012.69.

891 **Seiradake E,** Coles CH, Perestenko PV, Harlos K, McIlhinney RAJ, Aricescu AR, Jones EY.
892 2011. Structural basis for cell surface patterning through NetrinG–NGL interactions. The
893 *EMBO Journal* **30:**4479-4488. doi: 10.1038/emboj.2011.346.

894 **Sanders SJ,** He X, Willsey AJ, Ercan-Sencicek AG, Samocha KE, Cicek AE, Murtha MT,
895 Bal VH, Bishop SL, Dong S, Goldberg AP, Jinlu C, Keaney III JF, Klei L, Mandell JD,
896 Moreno-De-Luca D, Poultney CS, Robinson EB, Smith L, Solli-Nowlan T, Su MY, Teran
897 NA, Walker MF, Werling DM, Beaudet AL, Cantor RM, Fombonne E, Geschwind DH,
898 Grice DE, Lord C, Lowe JK, Mane SM, Martin DM, Morrow EM, Talkowski ME,
899 Sutcliffe JS, Walsh CA, Yu TW, Autism Sequencing Consortium, Ledbetter DH, Martin
900 CL, Cook EH, Buxbaum JD, Daly MJ, Devlin B, Roeder K, State MW. 2015. Insights into
901 Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. *Cell*
902 **87:**1215–1233. doi: 10.1016/j.neuron.2015.09.016.

903 **Shucard JL,** Lee WH, Safford AS, Shucard DW. 2011. The Relationship Between

Processing Speed and Working Memory Demand in Systemic Lupus Erythematosus: Evidence From a Visual N-Back Task. *Neuropsychology* **25:**45-52. doi: 10.1037/a0021218.

Song M, Zhou Y, Li J, Liu Y, Tian L, Yu C, Tianzi, J. 2008. Brain spontaneous functional connectivity and intelligence. *Neuroimage* **41:**1168-1176. doi: 10.1016/j.neuroimage.2008.02.036.

Skeide MA and Friederici AD. 2015. Response to Bornkessel-Schlesewsky *et al.* - towards a nonhuman primate model of language? *Trends in Cognitive Sciences.* **9:**483. doi: 10.1016/j.tics.2015.05.011.

Song YS, Lee H-J, Prosselkov P, Itohara S, Kim E. 2013. Trans-induced cis interaction in the tripartite NGL-1, netrin-G1 and LAR adhesion complex promotes development of excitatory synapses. *Journal of Cell Science* **126:**4926-4938. doi: 10.1242/jcs.129718.

Soto F, Watkins KL, Johnson RE, Schottler F, Kerschensteiner D. 2013. NGL-2 Regulates Pathway-Specific Neurite Growth and Lamination, Synapse Formation, and Signal Transmission in the Retina. *Journal of Neuroscience* **33:**11949-11959. doi: 10.1523/jneurosci.1521-13.2013.

Spellman T, Rigotti M, Ahmari SE, Fusi S, Gogos JA, Gordon JA. 2015. Hippocampal–prefrontal input supports spatial encoding in working memory. *Nature* **522:**309-314. doi: 10.1038/nature14445.

Steentoft C, Vakhrushev SY, Joshi HJ, Kong Y, Vester-Christensen MB, Schjoldager KTBG, Lavrsen K, Dabelsteen S, Pedersen NB, Marcos-Silva L, Gupta R, Bennett EP, Mandel U, Brunak S, Wandall HH, Levery SB, Clausen H. 2013. Precision mapping of the human *O*-GalNAc glycoproteome through SimpleCell technology. *Embo Journal* **32:**1478-1488. doi: 10.1038/emboj.2013.79.

Stepanyan A, Zakharyan R, Boyajyan A. 2013. The netrin G1 gene rs628117 polymorphism

929 is associated with ischemic stroke. *Neuroscience Letters* **549:**74-77. doi:
930 10.1016/j.neulet.2013.05.066.

931 **Stewart SE,** Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, Arnold PD, Evans
932 PD, Gamazon ER, Osiecki L, McGrath L, Haddad S, Crane J, Hezel D, Illman C,
933 Mayerfeld C, Konkashbaev A, Liu C, Pluzhnikov A, Tikhomirov A, Edlund CK, Rauch
934 SL, Moessner R, Falkai P, Maier W, Ruhrmann S, Grabe HJ, Lennertz L, Wagner M,
935 Bellodi L, Cavallini MC, Richter MA, Cook EH, Kennedy JL, Rosenberg D, Stein DJ,
936 Hemmings SMJ, Lochner C, Azzam A, Chavira DA, Fournier E, Garrido H, Sheppard B,
937 Umana P, Murphy DL, Wendland JR, Veenstra-VanderWeele J, Denys D, Blom R,
938 Deforce D, Van Nieuwerburgh F, Westenberg HGM, Walitza S, Egberts K, Renner T,
939 Miguel EC, Cappi C, Hounie AG, do Rosário MC, Sampaio AS, Vallada H, Nicolini H,
940 Lanzagorta N, Camarena B, Delorme R, Leboyer M, Pato CN, Pato MT, Voyiaziakis E,
941 Heutink P, Cath DC, Posthuma D, Smit JH, Samuels J, Bienvenu OJ, Cullen B, Fyer AJ,
942 Grados MA, Greenberg BD, McCracken JT, Riddle MA, Wang Y, Coric V, Leckman JF,
943 Bloch M, Pittenger C, Eapen V, Black DW, Ophoff RA, Strengman E, Cusi D, Turiel M,
944 Frau F, Macciardi F, Gibbs JR, Cookson MR, Singleton A for the North American Brain
945 Expression Consorium, Hardy J for the UK Human Brain Expression Database, Crenshaw
946 AT, Parkin MA, Mirel DB, Conti DV, Purcell S, Nestadt G, Hanna GL, Jenike MA,
947 Knowles JA, Cox N, Pauls DL. 2013. Genome-wide association study of obsessive-
948 compulsive disorder. *Molecular Psychiatry* **18:**788-798. doi: 10.1038/mp.2012.85.

949 **Stolfi A,** Ryan K, Meinertzhagen IA, Christiaen L. 2015. Migratory neuronal progenitors
950 arise from the neural plate borders in tunicates. *Nature* **527:**371-374. doi:
951 10.1038/nature15758.

952 **The Japanese Schizophrenia Sib-Pair Linkage Group (JSSLG)**, Arinami T, Ohtsuki T,
953 Ishiguro H, Ujike H, Tanaka Y, Morita Y, Mineta M, Takeichi M, Yamada S, Imamura A,

954 Ohara K, Shibuya H, Ohara, K, Suzuki Y, Muratake T, Kaneko N, Someya T, Inada T,
955 Yoshikawa T, Toyota T, Yamada K, Kojima T, Takahashi S, Osamu O, Shinkai T,
956 Nakamura M, Fukuzako H, Hashiguchi T, Niwa S, Ueno T, Tachikawa H, Hori T, Asada T,
957 Nanko S, Kunugi H, Hashimoto R, Ozaki N, Iwata N, Harano M, Arai H, Ohnuma T,
958 Kusumi I, Koyama T, Yoneda H, Fukumaki Y, Shibata H, Kaneko S, Higuchi H, Yasui-
959 Furukori N, Numachi Y, Itokawa M, Okazaki Y. 2005. Genomewide high-density SNP
960 linkage analysis of 236 Japanese families supports the existence of schizophrenia
961 susceptibility loci on chromosomes 1p, 14q, and 20p. *American Journal of Human*
962 *Genetics* **77:**937-944. doi: 10.1086/498122.

963 **The PsychENCODE** Consortium, Akbarian S, Liu C, Knowles JA, Vaccarino FM, Farnham
964 PJ, Crawford GE, Jaffe AE, Pinto D, Dracheva S, Geschwind DH, Mill J, Nairn AC,
965 Abyzov A, Pochareddy S, Prabhakar S, Weissman S, Sullivan PF, State MW, Weng Z,
966 Peters MA, White KP, Gerstein MB, Senthil G, Lehner T, Sklar P, Sestan N. 2015. The
967 PsychENCODE project. *Nature Neuroscience* **18:**1707-1712. doi: 10.1038/nn.4156.

968 **Thothathiri M. and Rattinger M.** 2015. Ventral and dorsal streams for choosing word order
969 during sentence production. *Proceedings of the National Academy of Sciences* **112:**15456-
970 15461. doi: 10.1073/pnas.1514711112.

971 **Ule J,** Ule A, Spencer J, Williams A, Hu JS, Cline M, Wang H, Clark T, Fraser C, Ruggiu M,
972 Zeeberg BR, Kane D, Weinstein JN, Blume J, Darnell RB. 2005. Nova regulates brain-
973 specific splicing to shape the synapse. *Nature Genetics* **37:**844-852. doi: 10.1038/ng1610.

974 **van Kuilenburg ABP,** Meijer J, Mul ANPM, Hennekam RCM, Hoovers JMN, de Die-
975 Smulders CEM, Weber P, Mori AC, Bierau J., Fowler B, Macke K, Sass JO, Meinsma R,
976 Hennermann JB, Miny P, Zoetekouw L, Vijzelaar R, Nicolai J, Ylstra, B, Rubio-Gozalbo
977 ME. 2009. Analysis of severely affected patients with dihydropyrimidine dehydrogenase
978 deficiency reveals large intragenic rearrangements of *DPYD* and a de novo interstitial

deletion del(1)(p13.3p21.3). *Human Genetics* **125:**581-590. doi: 10.1007/s00439-009-0653-6.

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH. 2011. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* **474:** 380-384. doi: 10.1038/nature10110.

Wang K, Zhang H, Bloss CS, Duvvuri V, Kaye W, Schork NJ, Berrettini W, Hakonarson H, the Price Foundation Collaborative Group. 2011. A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. *Molecular Psychiatry* **16:**949-959. doi: 10.1038/mp.2010.107.

Wilcox JA and Quadri S. 2014. Replication of NTNG1 association in schizophrenia. *Psychiatric Genetics* **24:**266-268. doi: 10.1097/ypg.0000000000000061.

Wise SP. 2008. Forward frontal fields: phylogeny and fundamental function. *Trends in Neurosciences* **31:**599-608. doi: 10.1016/j.tins.2008.08.008.

Wu JQ, Wang X, Beveridge NJ, Tooney PA, Scott RJ, Carr VJ, Cairns MJ. 2012. Transcriptome Sequencing Revealed Significant Alteration of Cortical Promoter Usage and Splicing in Schizophrenia. *PLoS One* **7**:e36351. doi: 10.1371/journal.pone.0036351.

Xu K, Schadt EE, Pollard KS, Roussos P, Dudley JT. 2015. Genomic and network patterns of schizophrenia genetic variation in human evolutionary accelerated regions. *Molecular Biology and Evolution* **32:**1148–1160. doi: 10.1093/molbev/msv031.

Yaguchi K, Nishimura-Akiyoshi S, Kuroki S, Onodera T, Itohara S. 2014. Identification of transcriptional regulatory elements for *Ntng1* and *Ntng2* genes in mice. *Molecular Brain* **7**:19. doi: 10.1186/1756-6606-7-19.

Yelin-Bekerman L, Elbaz I, Diber A, Dahary D, Gibbs-Bar L, Alon S, Lerer-Goldshtein T, Appelbaum L. 2015. Hypocretin neuron-specific transcriptome profiling identifies the sleep modulator Kcnh4a. *eLife* **4:**e08638. doi: 10.7554/eLife.08638.

Yin Y, Miner JH, Sanes JR. 2002. Laminets: Laminin- and netrin-related genes expressed in distinct neuronal subsets. *Molecular and Cellular Neuroscience* **19:**344-358. doi: 10.1006/mcne.2001.1089.

Yoon JH, Sheremata SL, Rokem A, Silver MA. 2014. Windows to the soul: vision science as a tool for studying biological mechanisms of information processing deficits in schizophrenia. *Frontiers in Psychology* **4**:A681. doi: 10.3389/fpsyg.2014.00681.

Zakharyan R, Boyajyan A, Arakelyan A, Gevorgyan A, Mrazek F, Petrek M. 2011. Functional variants of the genes involved in neurodevelopment and susceptibility to schizophrenia in an Armenian population. *Human Immunology* **72:**746-748. doi: 10.1016/j.humimm.2011.05.018.

Zhang B, Gaiteri C, Bodea LG, Wang Z, McElwee J, Podtelezhnikov AA, Zhang CS, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J, Emilsson V. 2013. Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer's Disease. *Cell* **153:**707-720. doi: 10.1016/j.cell.2013.03.030.

Zhang F, Shugart YY, Yue W, Cheng Z, Wang G, Zhou Z, Jin C, Yuan J, Liu S, Xu Y. 2015. Increased Variability of Genomic Transcription in Schizophrenia. *Scientific Reports* **5:**e17995. doi: 10.1038/srep17995.

Zhao M, Kong L, Qu H. 2014. A systems biology approach to identify intelligence quotient score-related genomic regions, and pathways relevant to potential therapeutic treatments. *Scientific Reports* **4**:A4176. doi: 10.1038/srep04176.

Zhou H, Hu S, Matveev R, Yu Q, Li J, Khaitovich P, Jin L, Lachmann M, Stoneking M, Fu Q, Tang K. 2015. A Chronological Atlas of Natural Selection in the Human Genome during the Past Half-million Years. *BioRxiv*. doi: 10.1101/018929.

1029 **Zhu Y,** Yang H, Bi Y, Zhang Y, Zhen C, Xie S, Qin H, He J, Liu L, Liu Y. 2011. Positive
1030 association between *NTNG1* and schizophrenia in Chinese Han population. *Journal of*
1031 *Genetics* **90:**499-502.