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ORIGINAL RESEARCH

Neurofibromatosis Type 1 Implicates Ras Pathways in the Genetic Architecture of Neurodevelopmental Disorders

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Abstract

The genetic architecture of neurodevelopmental disorders is largely polygenic, non-specific, and pleiotropic. This complex genetic architecture makes the search for specific etiological mechanisms that contribute to neurodevelopmental risk more challenging. Monogenic disorders provide an opportunity to focus in on how well-articulated signaling pathways contribute to risk for neurodevelopmental outcomes. This paper will focus on neurofibromatosis type 1 (NF1), a rare monogenic disorder that is associated with varied neurodevelopmental outcomes. Specifically, this paper will provide a brief overview of NF1 and its phenotypic associations with autism spectrum disorder, attention-deficit/hyperactivity disorder, and specific learning disorders, describe how variation within the *NF1* gene increases risk for neurodevelopmental disorders via altered Ras signaling, and provide future directions for NF1 research to help elucidate the genetic architecture of neurodevelopmental disorders in the general population.

Keywords Genetic architecture · Neurodevelopmental disorders · Neurofibromatosis type 1

Elucidating the genetic architecture of neurodevelopmental disorders is essential to try to understand the neurobiology underlying such phenotypes. The term 'genetic architecture' refers to the characteristics of genetic variation that influence phenotypic heritability (Mackay 2001; Timpson et al. 2018). In particular, it includes the number of genetic variants contributing to a given phenotype, the strength of their effects on a given phenotype, the frequency of those genetic variants in the population, and how they interact with one another and the environment (Gratten et al. 2014; Timpson et al. 2018). In contrast to heritability alone, genetic architecture refers to our broad understanding of all genetic factors and their mechanisms that influence a given phenotype (Timpson et al. 2018).

Fully articulating the genetic architecture of neurodevelopmental disorders has been challenging due to their largely polygenic, non-specific, and pleiotropic nature (Boyle et al. 2017; O'Donovan and Owen 2016; Watanabe et al. 2019). Large-scale twin and molecular genetic studies of neurodevelopmental disorders increasingly investigate the shared genetic underpinnings across disorders (Brain Consortium et al. 2018; Posthuma and Polderman 2013). For example, there is a considerable genetic overlap between autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), with genetic correlations ranging from 0.22 to 0.88 (Grove et al. 2019; Ghirardi et al. 2018; Lundström et al. 2011; Ronald et al. 2008, 2010, 2014). Genetic risk for ASD and ADHD is also shared with reading problems (Cederlöf et al. 2017; Verhoef et al. 2019), educational attainment (Demontis et al. 2019; Grove et al. 2019) and intellectual disability, among other outcomes (Demontis et al. 2019; Faraone et al. 2017). The strong genetic correlations indicate that neurodevelopmental disorders likely share common genetic pathways.

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Monogenic disorders present a unique opportunity to enrich our understanding of the genetic architecture of neurodevelopmental disorders in the general population. While monogenic disorders are biologically complex, they offer an opportunity to focus in on the multilevel sequelae of putative genetic pathways hypothesized to be affected in the disorder, which often result in varied neurodevelopmental outcomes. This approach may identify specific genetic pathways implicated in neurodevelopmental disorders in the general population and provide novel targets for intervention.

Neurofibromatosis type 1 (NF1) is a monogenic disorder that provides a model to understand how well-articulated genetic signaling pathways contribute to neurodevelopmental disorders more broadly (Acosta et al. 2012). The aims of this review are to: (1) provide a brief overview of NF1 and the associations between NF1 and ASD, ADHD, and specific learning disorders (SLD); (2) outline how pathogenic variation within the *NF1* gene increases risk for neurodevelopmental disorders via altered Ras signaling; and (3) provide future directions for NF1 research to help clarify the genetic architectures underlying neurodevelopmental disorders.

Neurofibromatosis type 1 (NF1)

NF1 is an autosomal dominant and fully penetrant genetic condition. It is estimated to affect about 1 in 2700–3000 live births (Evans et al. 2010; Uusitalo et al. 2015) and is characterized by café-au-lait macules, skinfold freckling, lisch nodules, neurofibromas, and neurodevelopmental disorders (National Institutes of Health 1988; Vogel et al. 2017; Williams et al. 2009). It is caused by mutations that occur in the *NF1* gene, at chromosome 17q11.2, which spans approximately 350 kb and 60 exons. To date, over 3000 different germline mutations within the *NF1* gene have been identified as pathogenic (Gutmann et al. 2017; Koczkowska et al. 2018). Approximately half of NF1 cases result from a spontaneous mutation and the other half of cases are familial (McKeever et al. 2008; Evans et al. 2010). The phenotypic expression of NF1 is highly variable making it difficult to predict prognosis (Rieley et al. 2011; Sites et al. 2019). Several mechanisms have been proposed to underlie the variable phenotypic expression, including allelic variation, epistatic interactions, second hit events in the *NF1* gene, modifying genes, epigenetic changes, and environmental influences (Easton et al. 1993; Rieley et al. 2011; Sites et al. 2019). See Gutmann et al. (2017) and Miller et al. (2019) for a more extensive review of the clinical phenotype in patients with NF1.

NF1 and neurodevelopmental disorders

NF1 is associated with increased risk for neurodevelopmental disorders compared to the general population (Acosta et al. 2006, 2012; Walsh et al. 2013; Torres Nupan et al. 2017; Vogel et al. 2017). This brief review will focus on the association between NF1 and ASD, ADHD, and SLD. Neuroimaging findings in NF1 are outside the scope of this paper. See Klein et al. (2017) and Payne et al. (2010) for reviews on this topic.

NF1 and autism spectrum disorder (ASD)

The prevalence rates of ASD symptomatology in individuals with NF1 range from about 10% to 40% (Eijk et al. 2018; Morris et al. 2016), as compared to 1.7% in the general population (Baio et al. 2018). Some studies, but not all (Garg et al. 2013), indicate that males with NF1 appear to be at slightly greater risk of developing ASD symptoms (1.6:1 to 2.68:1 sex ratio); however, this risk is smaller than the 4:1 sex ratio typically observed in general ASD samples (Garg et al. 2016; Morris et al. 2016). A recent study found that individuals with pathogenic NF1 mutations within the 3′ end of the *NF1* gene (between exons 34 and 57) had higher quantitative autistic trait severity, relative to individuals with a mutation in the 5′ end of the gene (Morris and Gutmann 2018); however, additional research is needed to explore mechanisms underlying this association.

NF1 and attention-deficit/hyperactivity disorder (ADHD)

Attention deficits are one of the most commonly reported concerns in children with NF1. Research indicates that between 38–67% of NF1 youth meet diagnostic criteria for ADHD (Hyman et al. 2005; Koth et al. 2000; Lidzba et al. 2012; Mautner et al. 2002), relative to 5.9% in the general population (Willcutt 2012). Studies within NF1 samples do not indicate increased rates of ADHD in males compared to females, as is seen in general ADHD samples (Acosta et al. 2006; Garg et al. 2013; Hyman et al. 2005; Koth et al. 2000; Lidzba et al. 2012). Additionally, executive functioning impairments are associated with ADHD in the general population (Willcutt et al. 2005) and are often identified in NF1 (Beaussart et al. 2018; Torres Nupan et al. 2017). Some research suggests that up to 70% of children with NF1 exhibit executive functioning deficits (Hyman et al. 2005; Payne et al. 2011). A recent meta-analysis found that working memory, planning/problem solving, inhibitory control, and cognitive

flexibility were the most common executive functioning deficits in NF1, in descending order of severity (Beaussart et al. 2018).

NF1 and specific learning disorders (SLD)

It is estimated that about 20–60% of individuals with NF1 meet criteria for a SLD (Ferner et al. 2007; Hyman et al. 2005), which is significantly higher than SLD rates in samples of unaffected siblings of individuals with NF1 (8%; Hyman et al. 2005), and in the general population (5–15%; American Psychiatric Association 2013). In particular, reading disorders are common in NF1 (Hyman et al. 2005; Vogel et al. 2017), with the phenotype involving cognitive processes implicated in dyslexia (Chaix et al. 2018; Cutting et al. 2000; Cutting and Levine 2010; Orraca-Castillo et al. 2014; Watt et al. 2008). Math disorders, or dyscalculia, also occur at a higher frequency in NF1 compared to the general population (Moore 2009; Orraca-Castillo et al. 2014).

Prioritizing NF1 for neurodevelopmental disorder research

The overlap between NF1 and neurodevelopmental disorders highlights the potential impact of pathogenic mutations in the *NF1* gene. Rare genetic disorders that achieve genome-wide association with a neurodevelopmental domain should be prioritized for research (Sanders et al. 2019). A genome-wide association threshold has been proposed that is based on the proportion of individuals with the neurodevelopmental disorder and a de novo protein truncating mutation in the same gene relative to the number of total cases, and the mutation rate/size of the gene (see Fig. 3 in Sanders et al. 2019). In the absence of available genome-wide association data, a population attributable risk estimate, which *estimates* the proportion of neurodevelopmental disorder cases due to a risk factor, like NF1, may serve as a preliminary indicator to prioritize rare genetic disorders for further study. Based on available estimates, *NF1* would likely surpass the threshold for genome-wide significant association with ASD, ADHD, and SLD (see Table 1). Although many

Table 1 Neurodevelopmental disorder population attributable risk due to NF1

ND	Prevalence of ND in general population (%)	Prevalence of ND in NF1 (%)	RR	AR	PAR (%)	Expected number of NF1 cases with de novo PTV in 100,000 ND cases
ASD	1.68[a]	10.9–39.2[b,c]	6.49–23.33	9.22–37.52	0.31–1.25	103–420
ADHD	5.90[d]	38.3–67.6[e,f]	6.49–11.46	32.40–61.70	1.08–2.06	363–691
SLD	9.70[g]	19.80–61.00[e,h]	2.04–6.29	10.10–51.30	0.34–1.71	113–575

RR, AR, and PAR estimates follow Fletcher and Wagner (1996). The crude RR estimate is derived from the prevalence rate of the neurodevelopmental disorder within NF1 divided by the prevalence rate of the neurodevelopmental disorder in the general population. AR is the prevalence rate of the neurodevelopmental disorder within the NF1 population minus the prevalence rate of the neurodevelopmental disorder in the general population. PAR is the attributable risk multiplied by .0$\bar{3}$, which is the estimated prevalence of NF1 in the general population (Uusitalo et al. 2015). The frequency of de novo NF1 cases, with a protein truncating mutation, within 100,000 neurodevelopmental disorder cases from the general population is estimated (Sanders et al. 2019). A crude estimate was derived by multiplying PAR by 100,000, multiplying the product by .42 as approximately 42% of NF1 cases are de novo (Evans et al. 2010) and multiplying that product by .8 as approximately 80% of NF1 cases have a protein truncating mutation (Upadhyaya and Cooper 1998). The range of RR, AR, and PAR estimates are based on the range of prevalence rates of neurodevelopmental disorders within NF1, reported in the literature. Despite the expected increased mutational rate of NF1, due to its large size, conservative estimates of the number of NF1 cases with de novo protein truncating variants would reasonably surpass the genome-wide significant association threshold (see Sanders et al. 2019)

ND neurodevelopmental disorder, *PTV* protein truncating variant, *ASD* autism spectrum disorder, *ADHD* attention-deficit/hyperactivity disorder, *SLD* specific learning disorder, *RR* relative risk, *AR* attributable risk, *PAR* population attributable risk

[a]Baio (2018)

[b]Morris (2016)

[c]Eijik (2018)

[d]Willcutt (2012)

[e]Hyman et al. (2005)

[f]Lidzba et al. (2012)

[g]Altarac and Saroha (2007)

[h]North et al. (1997)

rare genetic disorders are associated with increased risk for neurodevelopmental disorders (Zhu et al. 2014), NF1 demonstrates the qualities of a strong candidate for further neurodevelopmental disorder research. Further below, we provide examples of experimental models of NF1 which have provided the foundation for human clinical trials (see Cimino and Gutmann 2018 for a broader review of this). Taken together, NF1 is a very strong candidate to be prioritized for further study about mechanisms underlying these neurodevelopmental disorders.

Genetic, molecular and cellular mechanisms between NF1 and neurodevelopmental disorders

The *NF1* gene encodes for neurofibromin, a large 2818 amino acid protein which includes a small 300-residue domain structurally similar to GTPase-activating proteins (GAP; Gutmann et al. 2017). Particularly relevant to cognitive and behavioral outcomes in NF1, neurofibromin negatively regulates Ras activity (see Fig. 1; Diggs-Andrews and Gutmann 2013; Gutmann et al. 2017; Anastasaki and Gutmann 2014). Heterozygous pathogenic mutations in the *NF1* gene lead to decreased neurofibromin expression, or a truncated or nonfunctional protein, and increased cell growth and survival, leading to tumor development and cancer susceptibility (Basu et al. 1992; DeClue et al. 1991). *NF1* is expressed in a variety of cells, and especially in neurons and various glial cell types, including oligodendrocytes, astrocytes, and schwann cells (Daston et al. 1992; DeClue et al. 1991; Gutmann et al. 2017, 1991). *NF1* includes four alternatively spliced exons, 9a, 10a-2, 23a and 48a (Trovó-Marqui and Tajara 2006). In particular, *NF1* ex9a and *NF1* ex23a isoforms are highly expressed in the mouse brain and are linked to NF1 neurodevelopmental outcomes (Gutmann et al. 1999; Costa and Silva 2002). While *NF1* allelic variation is linked to *NF1* expression levels (Hoffmeyer et al. 1995), there is an absence of published *NF1* expression data in the developing human brain.

Ras pathways

Animal and human cellular models of NF1 are utilized to postulate mechanisms that underlie NF1 neurodevelopmental outcomes (see Schwetye and Gutmann 2014 for a review). This research implicates pathogenic mutations in *NF1* with increased Ras/RAF/MEK/ERK, AKT/mTOR and AC/cAMP signaling (see Fig. 1), and related alterations in GABAergic and dopaminergic functioning.

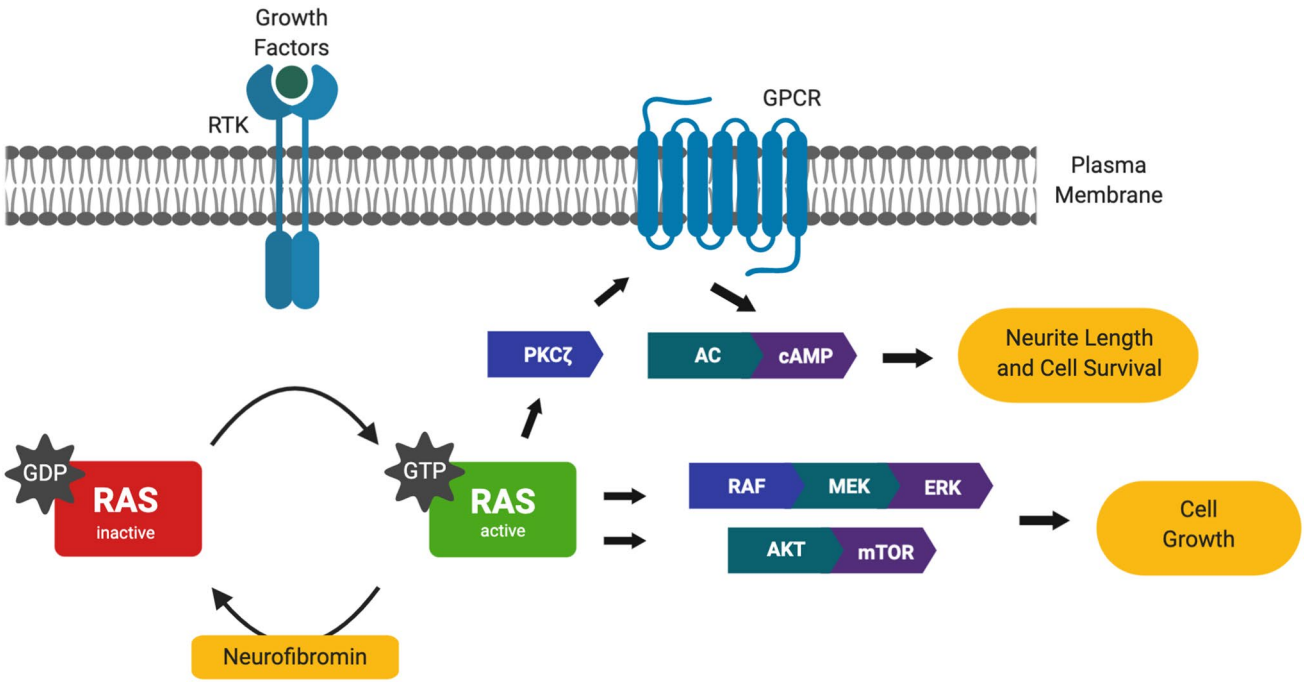

Fig. 1 Neurofibromin and Ras signaling pathways. Neurofibromin negatively regulates Ras activity by inactivating Ras-bound GTP, leading to inactive GDP-bound Ras. Activated Ras controls cell growth by affecting the RAF/MEK/ERK and Akt/mTOR pathways (Gutmann et al. 2017). Ras also positively regulates cyclic AMP (cAMP), via PKCζ activation of G protein-coupled receptors (GPCR) and activation of adenylyl cyclase (AC), which controls cell survival and neurite length in mammal neuronal cells (Anastasaki and Gutmann 2014). Pathogenic mutations *within* NF1 lead to increased Ras-ERK, Ras-mTOR, and Ras-cAMP signaling activity and increased cell growth and survival, and decreased axonal length. *ERK* extracellular signal-regulated kinase, *mTOR* mechanistic target of rapamycin

Ras/RAF/MEK/ERK pathway

Nf1 ± mice demonstrate enhanced ERK activity and increased GABA in presynaptic hippocampal neurons, with deficits in Long Term Potentiation (LTP), hippocampal plasticity and spatial learning (Costa et al. 2002; Cui et al. 2008). Lovastatin, an inhibitor of farnesyltransferase down-regulation of Ras activity, decreases Ras-ERK activity in the rodent brain and improves memory, learning and attention (Li et al. 2005). Decreasing Ras pharmacologically with GABA receptor blockers also improves memory, learning, and attention (Costa et al. 2002; Cui et al. 2008). Additionally, *Nf1* ± mice exhibit increased GABA/glutamate ratios in the prefrontal cortex and striatum as well as increased GABA (A) receptor density in the hippocampus, which indicates that different mechanisms may lead to GABAergic inhibition in different brain regions (Gonçalves et al. 2017). These findings have led to the hypothesis that NF1 may provide a model for the excitation/inhibition imbalance hypothesis in ASD (Foss-Feig et al. 2017) and ADHD (Kim et al. 2017). Here, the imbalance between glutamatergic and GABAergic processes, among other affected pathways, may explain altered neural activity and contribute to the cognitive and behavioral characteristics of ASD and ADHD.

RASopathies, or rare disorders caused by mutations in Ras-ERK pathway, broadly increase risk for neurodevelopmental disorders (Adviento et al. 2014; Pantaleoni et al. 2017; Pierpont and Wolford 2016; Vithayathil et al. 2018). RASopathies include Cardio-Facio-Cutaneous syndrome, Costello syndrome, Noonan syndrome and Legius syndrome. Further, common single nucleotide polymorphisms (SNPs) within RASopathy genes, and other SNPs that interact with Ras-ERK pathway genes, were found to be enriched in a general ASD sample (Mitra et al. 2017). Taken together, rare and common variation in Ras-ERK pathway genes are implicated in risk for neurodevelopmental disorders.

Akt/mTOR pathway

Decreased neurofibromin and increased Ras activation also lead to disruptions in the Akt/mTOR pathway (Lee and Stephenson 2007). The Akt/mTOR pathway regulates the cell cycle. In NF1, increased activation of the Akt/mTOR pathway is associated with poor prognosis of malignant peripheral nerve sheath tumors (Endo et al. 2013). The Akt/mTOR pathway also disrupts the cell cycle in other tissues and is implicated in megalencephaly and intracranial volume (Dobyns and Mirzaa 2019; Mirzaa et al. 2016; Reijnders et al. 2017). Indeed, approximately 50% of individuals with NF1 present with macrocephaly (Van Es et al. 1996), which is related to megalencephaly (Cutting et al. 2002; Said et al. 1996; Steen et al. 2001). A range of genetic variants that mildly activate the Akt/mTOR are associated with megalencephaly, intellectual disability, and ASD (Dobyns and Mirzaa 2019). Megalencephaly is also associated with intellectual disability (Reijnders et al. 2017) and ASD in the general population (Sokol et al. 2019). Transcriptomic dysregulation in the Akt/mTOR pathway is associated with ASD and brain/kidney cancers in the general population (Forés-Martos et al. 2019). Further, mice deficient for *Cntnap2,* a replicated ASD susceptibility gene (Anney et al. 2012), demonstrate hyperactive Akt/mTOR signaling in the hippocampus and showed ASD like behaviors (Xing et al. 2019). Treatment with Akt and mTOR inhibitors led to improved social behavior in mouse models (Xing et al. 2019). Consistent with findings in NF1, this demonstrates that ASD susceptibility genes identified in general ASD samples may increase Akt/mTOR signaling. Additionally, findings indicate that the Akt/mTOR pathway may alter neurodevelopmental vulnerability in both NF1 and general populations and may provide novel therapeutic targets.

Deficits in cAMP generation

Drosophila, mouse, and induced pluripotent stem cell (iPSC) NF1 patient derived neural cell models indicate that neurofibromin regulates cyclic AMP (cAMP) through Ras activation (Anastasaki and Gutmann 2014) and neuropeptide and G-protein stimulated adenylyl cyclase (AC) activity (Tong et al. 2002). *Nf1* ± mice exhibit decreased cAMP, which decreases neurite outgrowth and cone growth in hippocampal and retinal cells (Brown et al. 2010; Anastasaki and Gutmann 2014). Decreased cAMP concentration in brain tissue is a hypothesized risk for neurodevelopmental disorders in NF1 (Tong et al. 2002) and ASD in the general population (Kelley et al. 2008; Kim et al. 2017; Sethna et al. 2017). Increasing cAMP concentration pharmacologically rescues learning, but not memory problems, within an NF1 zebrafish model (Wolman et al. 2014) and memory in a Fragile X drosophila and mouse model (Choi et al. 2016).

NF1 molecular and cellular neurodevelopmental mechanisms have also been examined using iPSC NF1 patient derived neural cell models (Anastasaki et al. 2015; Sagata et al. 2017). Neural progenitor cells, derived via iPSC from NF1 cases, demonstrate increased Ras, decreased cAMP, and a reduction in dopamine levels (Anastasaki et al. 2015). Transcriptomic analysis indicates increased expression of genes involved in inhibiting apoptosis in NF1 males and control males (Sagata et al. 2017). This sex specific finding may also help to explain increased risk for ASD among NF1 males compared to NF1 females (Chisholm et al. 2018; Morris et al. 2016). Apoptosis may be disturbed in early stage neuronal cells within NF1, which may be one route to megalencephaly (Pirozzi et al. 2018). Finally, differences in gene expression are rescued by the administration of forskolin which activates adenylyl

cyclase (AC) and raises cAMP levels (Insel and Ostrom 2003) during early development (Sagata et al. 2017). Pharmacological increases in cAMP may help protect against ASD for those experiencing risk from this pathway (Sagata et al. 2017).

Impaired dopaminergic functioning

Mutations in the *NF1* gene also alter dopaminergic functioning. For example, an *Nf1* ± mouse model showed a reduction in striatal dopamine and selective and non-selective attention deficits, which normalized with the administration of methylphenidate or L-DOPA (Brown et al. 2010). Whole brain levels of dopamine, however, are not reduced in NF1 mouse models (Maloney et al. 2018). In addition, van der Voet et al. (2016) found that a NF1 drosophila model displayed a hyperactivity phenotype (nighttime locomotion) which was linked to impaired dopaminergic functioning, and was rescued with methylphenidate. In NF1 patient derived neurons via iPSC, the level of neurofibromin expression is positively associated with dopamine levels within NF1 cases (Anastasaki et al. 2015). Taken together, varied neurofibromin expression within NF1 samples impacts dopaminergic functioning which may predict risk for neurodevelopmental disorders, such as ADHD. Low dose methylphenidate improves objective measures of attention (Mautner et al. 2002) and ADHD behavioral symptoms in NF1 youth (Lion-François et al. 2014; Morris and Gutmann 2018). Additionally, effects of stimulant medication on ADHD symptoms within NF1 are comparable to those in the general ADHD population (Faraone and Buitelaar 2010). Despite similar outcomes for methylphenidate on NF1-ADHD and within general ADHD samples at a behavioral level, differences in brain functioning, doses, and side effects between NF1-ADHD and general ADHD samples have not been examined.

In summary, NF1 is implicated in several well-articulated Ras pathways (Ras/RAF/MEK/ERK; Akt/mTOR and AC/cAMP), as well as dopaminergic and GABAergic cell–cell signaling processes (see Schwetye and Gutmann 2014). In animal models, these Ras pathways are directly implicated in attention, spatial learning and memory, and have led to the development of novel pharmacological interventions for ASD, ADHD, and learning problems within NF1. Together, this research suggests that NF1, as a rare genetic disorder, should be prioritized to examine how Ras molecular pathways, and related dopaminergic and GABAergic signaling pathways, contribute to risk for neurodevelopmental disorders in the general population. Additionally, it highlights the potential role of therapeutic targets related to Ras signaling, which may generalize to a larger population. We will conclude by offering future directions for NF1 research.

Future research directions

Focus on sample stratification methods

Novel approaches to sample stratification may help to reduce phenotypic and etiological heterogeneity and narrow in on specific genetic pathways of risk. First, utilizing NF1 samples, or RASopathies samples more broadly, will help to constrain the genetic risk architecture for neurodevelopmental disorders on Ras pathways. Despite allelic variation within NF1, this approach yields a more genetically homogenous sample which may help to elucidate genetic variation that increases vulnerability for neurodevelopmental disorders (O'Donovan and Owen 2016). Population birth cohorts and NF foundations (e.g., Children's Tumor Foundation), patient registries (Seidlin et al. 2017), and NF mutation repositories (e.g., Koczkowska et al. 2019) may offer access to patients and genetic and phenotypic data for secondary analysis.

Second, selecting neurodevelopmental disorder samples from the general population based on an endophenotype may improve identification of specific genetic pathways of risk. For example, macrocephaly is an easily measured endophenotype, which may result from megalencephaly, and is found at increased rates within ASD (Stevenson et al. 1997) and NF1 (Van Es et al. 1996). Macrocephaly may result, in part, from *NF1* genetic variation that leads to impaired apoptosis in neuronal cells during early development (Pirozzi et al. 2018). A recent study conditioned ASD on macrocephaly which led to the identification of gene networks that are potentially disrupted and lead to brain overgrowth (Schafer et al. 2019), demonstrating utility in this approach. Additionally, Klein et al. (2019) demonstrated an enhanced ability to detect ADHD susceptibility loci by leveraging intracranial volume and other measures of regional brain anatomy size. Pathway analysis implicated genes involved in neurite outgrowth (Klein et al. 2019), which is associated with *NF1* via the Ras/Akt/cAMP pathway (Anastasaki et al. 2015).

Extend findings from NF1 to examine common variation in Ras pathways

Ras pathways implicated by NF1 may play an outsized role in the development of ASD, ADHD, and SLD. The genetic architecture of neurodevelopmental disorders consists of both rare and common variation in Ras pathways; however, it is possible that common and rare variation implicate different biological processes. For example, the types of genes identified by rare and common variant studies in schizophrenia are largely different genetic pathways

(Boyle et al. 2017). However, emerging evidence indicates that both rare and common variation within the Ras-ERK pathway is enriched in ASD samples (Adviento et al. 2014; Pantaleoni et al. 2017; Pierpont and Wolford 2016; Vithayathil et al. 2018; Mitra et al. 2017). This convergence of findings suggests that the Ras-ERK pathway may provide a therapeutic target for neurodevelopmental disorders for individuals with or without a Rasopathy.

Additionally, genome-wide association studies of ASD, ADHD, and SLD may examine for enrichment of Ras pathway genes. See Mitra et al. (2017) for a model on examining genetic variability for ASD in the general population and RASopathies samples. Researchers interested in this approach may consider utilizing the National Cancer Institute Ras Pathway 2.0 gene set which includes 227 genes (McCormick 2015). Expression in the human brain for each gene in this pathway was verified with Allen Brain Atlas (Hawrylycz et al. 2012) and GTEx Portal (Carithers and Moore 2015) on 11/12/2019. Additionally, the use of protein interaction bioinformatic tools such as STRING (Szklarczyk et al. 2015) will further help to prioritize genes which are functionally related to *NF1*. Combining bioinformatic methods with functional enrichment approaches, like partitioned LD score regression (Finucane et al. 2015), will allow researchers to examine if the *NF1* related molecular pathways are enriched in idiopathic neurodevelopmental disorders.

Finally, future genetic studies with NF1 samples may leverage ADHD and ASD polygenic scores derived from the general population (Alemany et al. 2019) to examine the role of common neurodevelopmental susceptibility variants in contributing to risk in this population. If the genetic architecture for neurodevelopmental disorders is similar both within NF1 and outside of NF1, then drug-discoveries for NF1 may more easily extend to the general population.

Advancing from *NF1* to molecular and cellular outcomes to guide treatment

Functional studies involving NF1 animal and induced pluripotent stem cell (iPSC) NF1 patient derived neural cell models are needed to further detail the downstream effects of variation in the *NF1* gene. In particular, more studies involving functional modeling of the role of allelic variation in *NF1* and interaction of *NF1* variants with different genetic backgrounds are needed to understand phenotypic variability within NF1 (see Wegscheid et al. 2018; Zhu et al. 2014). Such research may also shed light on the genetic architecture of neurodevelopmental disorders in the general population, especially if *NF1* related pathways are implicated.

NF1 animal models are critical for detailing molecular and cellular pathways implicated in neurodevelopmental disorders within this population. For example, *Nf1* ± mice demonstrated increased GABA, decreased long term potentiation and decreased hippocampal dopamine which was associated with learning difficulties (Costa et al. 2002; Cui et al. 2008; Wegscheid et al. 2018). Such findings have led to the discovery of Lovastatin as a possible drug to target attention and learning problems in the context of NF1 (Li et al. 2005). Lovastatin rescued long-term potentiation and spatial learning deficits in *Nf1* ± mice, however, Lovastatin and Simvastatin trials in youth with NF1 did not alter attention, intelligence, or visual spatial learning (Payne et al. 2016; van der Vaart et al. 2013). One way to enhance the translations of effective intervention from NF1 animal models to humans may be shifting the therapeutic target. Due to the complex differences in behavioral measurement across species, interventions which effectively target cross-species biomarkers related to functional human outcomes should be prioritized (Acosta 2013; Sahin et al. 2018). For example, with resting-state functional connectivity MRI, striatal dysfunction and disrupted corticocortical connectivity in the default network is evident across Nf1 ± mice and individuals with NF1 (Shofty et al. 2019). These neurodevelopmental outcomes provide a similar therapeutic target across species. Indeed, resting state fMRI measures were also improved in pilot studies of Cogmed (Yoncheva et al. 2017) and Lovastatin (Chabernaud et al. 2012). Additionally, using transcranial magnetic stimulation, it was observed that lovastatin decreased intracortical inhibition, increased synaptic plasticity, and increased phasic alertness in adults with NF1 (Mainberger et al. 2015). Thus, future research should examine similarities in pathophysiology underlying neurodevelopmental risk in NF1 animal models and humans.

Human cell lines in NF1 allow the effects of allelic variation and genetic background on cellular phenotypes to be investigated on a much larger scale (Wegscheid et al. 2018). For example, the use of multi-electrode arrays within iPSC studies will allow for the neural cellular phenotypes within NF1 to be examined (see Deneault et al. 2019 for example in ASD). Additionally, cerebral organoids provide another way to examine neurodevelopmental processes which are disrupted in NF1 and may provide a model for more general pathways to neurodevelopmental disorder risk. For example, cerebral organoids derived from iPSCs from individuals with ASD show an accelerated cell-cycle and increased GABAergic inhibitory neuron production, which is related to increased *FOXG1* expression (Mariani et al. 2015). *FoxG1* also inhibits apoptosis, a process that is mediated by the PI3K/Akt/mTOR pathway. Interestingly, findings from idiopathic ASD-derived organoids (Mariani et al. 2015) are consistent with increased Ras-ERK and Ras-mTOR activation within NF1 (see Fig. 1). Cellular or organoid phenotypes within NF1 and other neurodevelopmental disorders may provide a way to reduce etiological and phenotypic

heterogeneity in these populations, allowing for the identification of more refined genetic architectures.

Finally, our understanding of *NF1* expression in brain tissue is limited to animal models and iPSC cells. For example, in a mouse model, the *NF1 ex 9a* isoform is associated with learning, expressed exclusively in neurons, especially in the cortex, hippocampus, striatum and septum during early postnatal development (Gutmann et al. 1999). Similarly, mouse models without *NF1* ex23a show deficits in hippocampal learning as well as motor delays; however, this isoform tends to be more highly expressed in astrocytes (Costa et al. 2001). Findings from these models need to be connected back to the human brain. *NF1* expression patterns in the developing human brain can be examined through gene expression brain atlases (e.g., Allen Brain Atlas). Such analyses will provide a baseline for *NF1* and related Ras pathway gene expression across time, region of the brain and cell type. Brain organoids and assembloids also provide an opportunity to examine expression of *NF1* in human brain tissue. Incorporating CRISPR-Cas9 methods with these three-dimensional cultures, allows for the ability to examine how *NF1* allelic variation effects cell structure and function.

Conclusion

NF1 provides a unique opportunity to investigate specific genetic pathways that contribute to the genetic architecture underlying neurodevelopmental disorders in the general population. The well-defined molecular pathways implicated in neurodevelopmental disorders within NF1, such as Ras/RAF/MEK/ERK, Akt/mTOR and AC/cAMP, may inform the development of novel therapeutics, which benefit a broader population. In sum, NF1 provides a model to help us to better understand the etiological and phenotypic heterogeneity within neurodevelopmental disorders, which complements other methodological approaches focused on refining genetic architecture.

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Compliance with ethical standards

Conflict of interest Jessica A. Kaczorowski, Taylor F. Smith, Amanda M. Shrewsbury, Leah R. Thomas, Valerie S. Knopik and Maria T. Acosta declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

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