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EDITORIAL

From vulnerability to protection: The dual nature of ADNP variants

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In this second issue of *Genomic Psychiatry* (1), we highlight a report by Illana Gozes and her team from Tel Aviv as our cover article. In an in-depth Genomic Press interview published in *Brain Medicine* (2), Gozes provided insights into her body of work on activity-dependent neuroprotective protein (ADNP) (3). Her research demonstrated ADNP's essential role in brain formation, neurodevelopment, gene regulation, and protein interactions. She identified ADNP's involvement in autophagy, schizophrenia, and autism through critical binding with SHANK3 and actin. In the report published in this issue, her team presents new original data that challenges the conventional narrative surrounding genetic variation (4). The authors identified a novel variant of ADNP. What sets this apart is the molecular insight it provides and the philosophical ramifications it bears about the nature of genetic determinism. Moreover, we can see here in one person what may be happening at the population level: beneficial variants make deleterious molecular evolution less deleterious.

ADNP was first identified in Gozes' lab over two decades ago, and its role as critical for cerebral development is now well established (5). Pathogenic variants in this single gene have frequently been associated with clinical phenotypes across neurodevelopmental, neuropsychiatric, and neurodegenerative spectra. At the severe end of this clinical arc lies Helsmoortel-Van Der Aa syndrome—colloquially referred to as ADNP syndrome—a disorder marked by de novo loss-of-function pathogenic variants in ADNP and characterized by profound developmental impairments.

Yet a glimmer of biological resilience emerges amid that bleak landscape of pathology. Gozes and colleagues have now identified an inherited ADNP variation—ADNP_Glu931Glyfs12—that, paradoxically, appears to confer protection rather than deficit (see Figure 1 for a conceptual representation). This variant was discovered in a mother (VB) whose adaptive functioning, measured via the rigorous Vineland Adaptive Behavior Scales, surpassed population averages. Her son (HB), who inherited this same (protective) variant alongside a *de novo* pathogenic ADNP variant (p.Arg730Thrfs*5), demonstrated a clinical phenotype far milder than would be expected in the context of a dual-mutant ADNP profile. That finding alone would be noteworthy; the mechanisms behind it elevate it to the realm of scientific provocation. Of note, Chen et al. predicted that in evolutionary terms, beneficial mutations partially negatively offset deleterious mutations. Their outstanding paper is entitled "From Drift to Draft: How Much Do Beneficial Mutations Actually Contribute to Predictions of Ohta's Slightly Deleterious Model of Molecular Evolution?" (6). Essentially, Chen et al. conclude that the deleterious model of molecular evolution is indeed ultimately deleterious. However, it would have been even more deleterious had it not been for the compensating effects of beneficial variants – which is exactly the case with VB's son. It is highly thought-provoking that Gozes's findings illustrate in a single case what may be happening much more broadly population-wise.

Using advanced structural modeling and molecular analyses, they show that the protective variant creates a new binding motif for 14-3-3 proteins—a family of central chaperones of intracellular traffic and signaling. More notably, this variant seems to enhance the interaction between ADNP and NAPVSIPQ (NAP), an endogenously occurring neuroprotective peptide within the ADNP sequence that has been developed as davunetide and studied in clinical trials. Essentially, the variant does not just "escape harm"—it tunes the protein-protein and internal protein interaction networks in ways that increase functional resilience.

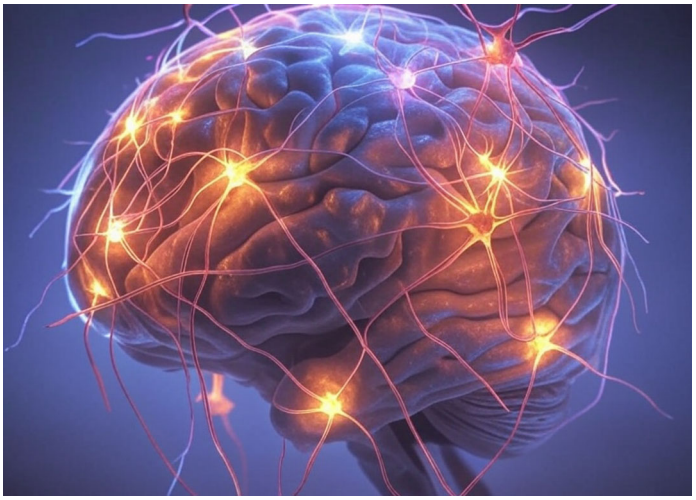

Figure 1. A conceptual illustration of a brain with glowing neurons forming a protective network. This is inspired by Gozes et al.'s findings, where the ADNP_Glu931Glyfs*12 mutation enhances neuroprotection and resilience against pathogenic variants in neurodevelopmental disorders (4). Image generated by Grok (xAI, 2025) with active author input.

Such findings have caused me to rethink my assumptions. Frameshift mutations have long been conceptualized as detrimental and disruptive events; however, in rare cases, they may create new functional motifs that enhance, rather than impair, protein function. This is far more than just a technical distinction. It redefines how we conceptualize genetic architecture—not as a binary of health versus disease, but as a complex continuum where certain disruptions yield unanticipated advantages. We can almost see the theory of evolution in action here: some rare, random variants offer advantages and may be selected over generations.

The implications are immense. Protective mutations—rare genetic chance events that give their carriers a biological leg up— have historically gotten less play than pathogenic ones. In 2010 H. Allen Orr stated that "the population genetic study of advantageous mutations has lagged behind that of deleterious and neutral mutations" (7). Yet they might provide the key to therapeutic mimicry. So if nature, via evolutionary happenstance, makes variants that buffer against disease, then

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pharmacological approaches that mimic these configurations might be both possible and profoundly effective. Sane et al. have recently shown that "shifts in mutation spectra may evolve under selection and can directly alter the outcome of adaptive evolution by facilitating access to beneficial mutations" (8).

The Gozes report pays tribute as much to structural biology as to translational imagination. The team's computational models provide a visual and mechanistic bridge from sequence variation to phenotypic outcome, illustrating how a structure-function analysis converts genotype into actionable insight. Identifying enhanced interactions with 14-3-3 and SH3 domains further solidifies that specific variants do not exist in isolation; they participate in protein crosstalk that may rewire entire signaling pathways.

This case, elegant in its anomaly, also illustrates the staggering complexity of neurodevelopmental syndromes. Within the same gene—ADNP—mutational heterogeneity produces wildly divergent clinical trajectories. It is precisely this variance that underscores the urgency of precision medicine. The patient is not the variant but the sum of variants, modifier genes, and environment. Only by mapping this intricate constellation can we hope to intervene with precision.

The therapeutic echo of this study is most palpable in its rekindling of interest in davunetide. Long investigated as a neuroprotective agent in murine models and human trials, its interaction with the pathway modulated by the protective variant breathes new relevance into its pharmacologic trajectory. Could the efficacy of davunetide in broader clinical populations be sharpened in genetically defined subgroups? The data suggest so.

Interestingly, cerebrospinal fluid biomarkers of synaptic dysfunction, including 14-3-3 are altered in Parkinson's disease and related neurodegenerative tauopathies (9), with tauopathies being targeted in previous davunetide clinical trials. Further speaking of genetic differences, one that is glaring and often ignored is sex differences. Importantly, in collaboration with the Toyo-Oka group, the Gozes group showed that the cytoplasmic localization of ADNP through 14-3-3 promotes sex-dependent neuronal morphogenesis, cortical connectivity, and calcium signaling (10). In this respect, the Gozes group further discovered unexpected sex differences in the pure neurodegenerative tauopathy progressive supranuclear palsy (PSP), revealing faster deterioration in women. Sex stratification of a placebo-controlled Phase 2/3 study clinical trial results showed that davunetide offers statistically significant neuroprotective benefits in female subjects in one of the co-primary endpoints of the study, the Schwab and England Activities of Daily Living (SEADL) scale. Analysis of the second co-primary endpoint, PSP Rating Scale (PSPRS), revealed that while davunetide had trending beneficial effects in the female subject population, the male subject population showed a statistically significant deterioration compared to placebo, strongly indicating a sex-based effect of davunetide (11). As such, ExoNavis Therapeutics Ltd. Is developing davunetide for women suffering from PSP (12).

Furthermore, the Gozes group recently showed that ADNP is essential for sex-dependent hippocampal neurogenesis, through male unfolded protein response and female mitochondrial gene regulation, with davunetide's protection (13). As such, davunetide is further being developed for ADNP syndrome (ExoNavis).

From a future bold strategic vantage, the next steps are clear. A deeper structural interrogation of ADNP variants—pathogenic and protective—is needed. Simultaneously, the identification of small molecules that enhance 14-3-3 or SH3 domain interactions opens fertile ground for drug development. These are not marginal pursuits; they represent a conceptual pivot from reactive medicine toward anticipatory design.

There is, too, a personal resonance. My own work on the leptin pathway—initially a narrow investigation into an exceedingly rare obesity syndrome—ultimately revealed principles central to metabolism, behavior, and endocrine regulation (14, 15). In a similar fashion, this single protective ADNP variant may illuminate pathways fundamental to cognition, synaptic integrity, and neuroprotection. The outlier is often the oracle.

This study, in its fusion of molecular rigor and clinical nuance, reminds us that genetic diagnoses are not deterministic verdicts. They are dynamic starting points. What matters is the context—the precise nature of the variant, the background in which it occurs, and the downstream networks it engages or disrupts. The ADNP_Glu931Glyfs*12 variant is not a glitch. It is, rather astonishingly, a protective signature written in the language of error.

At its core, this work reaffirms the elegance of molecular neuroscience—the beauty of watching molecular shifts ripple into human behavior and the audacity of attempting to understand the mind by interrogating the molecule. In the confluence of computational modeling, genetic analysis, and clinical observation, we are reminded of what genomic psychiatry at its best can achieve.

As we advance into an era where we no longer ask what a gene does in general but rather what it does in a particular patient, the Gozes paper emerges as a case study of scientific creativity and biological humility. It suggests that not all genetic mistakes are errors. Some are innovations—quiet revolutions etched into the genome, awaiting discovery.

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