Mechanistic Architecture of Psychosis in 22q11.2 Deletion Syndrome: A Systems-Level Model

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The 22q11.2 deletion syndrome presents a paradox fundamental to psychiatric genetics: individuals harboring identical hemizygous deletions spanning approximately 46 genes exhibit profound phenotypic heterogeneity, with only 25-40% developing psychotic disorders despite uniform genetic architecture (Murphy et al., 1999; Schneider et al., 2014).

This incomplete penetrance, juxtaposed against a 20-30-fold elevation in psychosis risk relative to the general population, positions 22q11.2DS as an unparalleled natural experiment for dissecting the molecular cascades linking genetic variation to psychiatric phenotypes.

Rather than reflecting haploinsufficiency of a single master regulator, psychosis in 22q11.2DS emerges through convergent disruption of multiple interacting pathways that create a state of coordinated vulnerability across mitochondrial energetics, immune homeostasis, blood-brain barrier integrity, and excitatory-inhibitory balance.

The critical insight from recent systems-level investigations is that psychosis does not arise from the deletion per se, but from the failure of compensatory mechanisms to maintain homeostasis when these interconnected systems are simultaneously challenged during adolescent neurodevelopment.

The Mitochondrial Foundation: From Bioenergetic Insufficiency to Synaptic Collapse

MRPL40 and the Mitochondrial Translation Machinery

Among the 40-60 genes within the typical 3.0 Mb deletion, seven encode mitochondrial-localizing proteins, with MRPL40 (mitochondrial ribosomal protein L40) emerging as a critical mechanistic lynchpin. MRPL40 participates in the assembly of the mitochondrial ribosome, which translates the 13 protein-coding genes of the mitochondrial genome - all essential components of the oxidative phosphorylation (OXPHOS) machinery.

The specificity of MRPL40's impact is remarkable: haploinsufficiency does not affect mitochondrial ultrastructure, DNA content, or presynaptic distribution, but instead produces a selective deficit in mitochondrial DNA-encoded protein translation (Devaraju et al., 2017; Li et al., 2019).

iPSC-derived neurons from 22q11.2DS patients with schizophrenia demonstrate ~50% reduction in ATP levels, with corresponding decreases in electron transport chain complex I and IV activities (Li et al., 2019).

The correlation between affected ETC complexes and their mitochondrial-encoded protein content is mechanistically revealing: complexes I and IV, which contain seven and three mitochondrial-encoded subunits respectively, show substantial deficits, while complexes II and III (containing zero and one mitochondrial-encoded subunits) remain functionally intact.

An isogenic iPSC line with heterozygous MRPL40 truncation recapitulated the patient phenotypes: reduced levels of MT-ND1, cytochrome b, and COX1; decreased complex I and IV activities; and ~30% ATP reduction (Li et al., 2019).

The functional consequences extend to mitochondrial calcium handling through dysregulation of the mitochondrial permeability transition pore (mPTP). Two-photon calcium imaging revealed that high-frequency stimulation (80 Hz) produces abnormally elevated calcium transients in both presynaptic cytosol and mitochondrial matrix of Mrpl40+/- neurons (Devaraju et al., 2017).

The mPTP inhibitor bongkrekic acid phenocopied these deficits in wild-type mice but produced no additional effect in mutants, establishing mPTP-dependent calcium extrusion failure as the proximal mechanism. This finding is particularly significant because it demonstrates that MRPL40 haploinsufficiency creates a specific calcium handling deficit that compromises synaptic function even before generalized bioenergetic failure manifests.

The Mitochondrial Interactome and Second-Order Effects

The deletion's impact on mitochondrial function extends beyond MRPL40 through a coordinated network of haploinsufficient genes. Quantitative mass spectrometry on patient-derived fibroblasts and Df(16)A+/- mouse brains revealed highly significant perturbations centered on SLC25A1 (citrate/malate antiporter) and SLC25A4 (ADP/ATP translocase) - neither encoded within 22q11.2 but functionally coupled to deleted genes MRPL40 and TXNRD2 (thioredoxin reductase 2) (Gokhale et al., 2019).

SLC25A1 levels were reduced ~30% in patient fibroblasts, with compensatory SLC25A4 decreases (~25%), impairing citrate export and malate import. This disrupts the malate-aspartate shuttle, compromising cytosolic NADH regeneration and potentially limiting glycolytic flux to support neurotransmitter synthesis and vesicle recycling - both ATP-intensive processes critical for synaptic function.

Additional mitochondrial genes within the deletion amplify oxidative stress vulnerability: SLC25A1 impairs citrate export, depleting NADPH for glutathione regeneration; TXNRD2 weakens thioredoxin-based ROS scavenging, elevating H_2O_2 by 2-fold; TANGO2 disrupts acyl-CoA metabolism, promoting mitochondrial fission via

DRP1 hyperactivation; ZDHHC8 alters palmitoylation of FIS1/MFN2, unbalancing fusion/fission dynamics; and UFD1 impairs ubiquitin-mediated mitophagy, allowing damaged organelles to accumulate (Gokhale et al., 2019; Kolar et al., 2023).

In aggregate, these perturbations produce a 30-50% drop in ATP/ROS ratio in hippocampal neurons, sensitizing cells to calcium overload and creating conditions for excitotoxicity.

Mitophagy Failure: The Critical Determinant of Penetrance

The differential penetrance of psychosis in 22q11.2DS hinges not on baseline mitochondrial function - which is compromised in all deletion carriers - but on the capacity for mitochondrial quality control through mitophagy. iPSC-derived neurons from patients with schizophrenia exhibit depolarized mitochondria alongside aged mitochondrial protein populations, indicating severely impaired mitochondrial turnover (Stronati et al., 2024).

Using a mitochondrially-targeted timer protein that shifts fluorescence from green to red over 8-16 hours, investigators demonstrated that psychotic individuals harbor significantly older mitochondrial populations compared to both neurotypical controls and non-psychotic deletion carriers. Remarkably, the non-psychotic group shows the youngest mitochondrial populations, suggesting compensatory upregulation of mitochondrial biogenesis and turnover.

The mechanism underlying this divergence centers on lysosomal dysfunction. Neurons from psychotic individuals display elevated lysosomal pH and reduced proteolytic activity, as measured by DQ-BSA hydrolysis assays (Stronati et al., 2024). This pH elevation creates a pathological feedback loop: depolarized mitochondria are successfully targeted to autophagolysosomes via PINK1-Parkin signaling, but degradation stalls at elevated pH, leading to accumulation of dysfunctional mitochondria within lysosomes.

The resulting energetic insufficiency appears to trigger nuclear suppression of mitochondrial biogenesis through reduced PGC-1α, PGC-1β, PPARα, and PRKN expression - a maladaptive response that further depletes functional mitochondrial mass (Li et al., 2021).

Critically, treatment with poly-DL-lactide-co-glycolide acidifying nanoparticles restored lysosomal pH, normalized proteolytic activity, reduced the population of depolarized mitochondria, and rejuvenated the mitochondrial protein pool in neurons from psychotic individuals (Stronati et al., 2024).

This rescue demonstrates that the mitochondrial phenotype represents a failure of homeostatic regulation rather than irreversible structural damage, and suggests that mitophagy enhancement could constitute a disease-modifying therapeutic intervention.

The non-psychotic 22q11.2DS individuals who successfully avoid psychosis appear to compensate through upregulation of nuclear-encoded (NDUFV1, NDUFV2) and mitochondrial-encoded (MT-ND1, MT-ND2, MT-ND4, MT-CYB, MT-CO1, MT-ATP6, MT-ATP8) electron transport chain genes, increasing mtDNA copy number and expression of biogenesis regulators (Li et al., 2021).

This compensatory mitochondrial biogenesis represents a critical resilience mechanism, and its failure - due to additional genetic variants, environmental stressors, or stochastic processes - precipitates the cascade toward psychosis.

Transcriptional Dysregulation: DGCR8 and the MicroRNA Network

Global MicroRNA Depletion and Developmental Timing

DGCR8 haploinsufficiency emerges as a master regulator of dysfunction with cascading consequences across neurodevelopment. As the RNA-binding component of the microprocessor complex, DGCR8 mediates pri-miRNA to pre-miRNA conversion; its reduction by 50% creates a gradient of miRNA dysregulation affecting hundreds of target genes. Rao et al. (2025) documented 15 downregulated miRNAs in patient-derived dorsal forebrain organoids, including hsa-mir-185 - itself encoded within 22q11.2.

MirNet analysis revealed that targets of these depleted miRNAs significantly overlapped with upregulated genes in cycling progenitors (24% of upregulated genes, $P = 0.03$), particularly those regulating cell cycle progression.

The most striking cellular phenotype is not aberrant cell fate specification but rather a fundamental slowing of neurodevelopmental tempo. Pseudotime trajectory analysis demonstrated that patient-derived organoid cells accumulate disproportionately in early progenitor states while showing depletion in terminal differentiation phases ($P = 1.35x10^{-11}$ at day 70) (Rao et al., 2025).

Immunostaining confirmed significantly elevated Ki67+/SOX2+ cycling neural progenitor cells ($P = 0.04$), and PIP-FUCCI cell cycle analysis revealed G1 phase accumulation (1.35-fold increase, $P = 0.037$) with S phase depletion (0.58-fold decrease, $P = 0.045$). Neurosphere differentiation assays provided direct evidence: only ~20% CTIP2+ neurons emerged from patient cultures versus ~40% in controls ($P < 0.01$).

This developmental asynchrony has profound implications for cortical architecture. The human cortex undergoes rapid expansion during mid-gestation, with peak neurogenesis occurring at 14-20 gestational weeks.

If 22q11.2 deletion reduces the rate of progenitor-to-neuron transition even modestly - increasing cell cycle length by 10-15% - the cumulative effect over this window would produce substantial reductions in neuronal output, particularly affecting late-arriving upper cortical layer neurons that form long-range associative connections essential for higher cognitive functions.

Latent time trajectory analysis exposed three distinct patterns of dysregulation: genes persistently upregulated from progenitors through mature neurons (EMC10, PEG3 - negative regulators of neurogenesis), those transiently elevated in early stages (TCF3), and those induced late (MAP4K4, SOX11, TCF4 - inhibitors of neurite outgrowth) (Rao et al., 2025).

This temporal complexity suggests DGCR8 haploinsufficiency doesn't merely reduce miRNA abundance; it fundamentally desynchronizes developmental gene expression programs, creating neurons with altered molecular identities and reduced connectivity

potential.

Synaptic Gene Dysregulation in Mature Neurons

Transcriptional perturbations are most pronounced and most relevant to schizophrenia heritability in mature neurons. LD score regression revealed 1.20-fold heritability enrichment ($\tau c = 1.0x10^{-8}$, adjusted P = 0.01), driven predominantly by upregulated genes (1.31-fold enrichment, $\tau c = 1.96x10^{-8}$, adjusted P = 0.001) (Nehme et al., 2022).

Among 434 differentially expressed genes across developmental stages, 89% mapped outside the deleted region - a remarkable trans-acting effect demonstrating that haploinsufficiency of genes within 22q11.2 cascades to alter genome-wide expression patterns.

In neural progenitor cells, MEF2C was significantly upregulated. MEF2C is an activity-dependent transcription factor that negatively regulates excitatory synapse number and is normally repressed by TBX1; its derepression due to TBX1 haploinsufficiency likely initiates a cascade limiting synaptogenic capacity (Nehme et al., 2022).

In mature neurons, upregulated genes showed striking enrichment for synaptic vesicle cycling (GO:0099504, q = 0.001), with 193 of 2,173 upregulated transcripts possessing SynGO synaptic annotations. However, downregulated genes were enriched for presynaptic functions, and proteomic validation confirmed reduced abundance of SV2A, NRXN1, and SYT11 - all rare variant schizophrenia risk genes (Nehme et al., 2022).

This creates a paradoxical situation: transcriptional upregulation of synaptic genes fails to normalize protein stoichiometry at synapses, suggesting attempted but inadequate homeostatic responses.

The enrichment of idiopathic schizophrenia risk variants in genes dysregulated in 22q11.2DS neurons (SCHEMA loss-of-function variants enriched at $P = 5.08x10^{-6}$; MAGMA competitive analysis $P = 7.93x10^{-8}$) demonstrates that common and rare variants may act on overlapping biological processes illuminated at high resolution in 22q11.2DS (Nehme et al., 2022).

MicroRNA-Mediated Neurotransmitter Receptor Dysregulation

The DGCR8-driven miRNA depletion has specific consequences for neurotransmitter receptor expression. Reduced miR-338-3p elevates dopamine D2 receptor (DRD2) expression, enhancing thalamocortical dopaminergic signaling and inducing adolescent synaptic defects (Zinkstok et al., 2019). DGCR8 also regulates miR-185, which modulates immune responses and derepresses genes like GRM8 (metabotropic glutamate receptor 8), disrupting glutamatergic long-term potentiation (Michaelovsky et al., 2019).

At the neuronal level, miR-223 - elevated in orbitofrontal cortex of schizophrenia patients (correlating with SERPINA3; r=0.402, p=0.006) - targets GRIN2B (NR2B; r=-0.431, p=0.003) and GRIA2 (GluR2; r=-0.481, p<0.001), reducing mRNA levels (Amoah et al., 2020). Astrocytic exosomes transfer miR-223 to neurons, doubling neuronal levels and suppressing Grin2b/Gria2; LNA inhibitors rescue this effect. Downregulated ADAR1/ADAR2 (inverse to miR-223) enhances miRNA processing,

amplifying these effects.

Indirectly, miR-223 correlates negatively with GAD1 (r=-0.380, p=0.008), linking to GABA synthesis deficits (Amoah et al., 2020).

Excitatory-Inhibitory Imbalance: The Hippocampal-Prefrontal Circuit Dysfunction

PRODH and Proline-Mediated GABAergic Dysfunction

PRODH (proline dehydrogenase) haploinsufficiency introduces a metabolic perturbation with direct consequences for inhibitory neurotransmission. PRODH catalyzes the first step in proline catabolism in the mitochondrial matrix, converting L-proline to Δ1-pyrroline-5-carboxylate while regenerating $FADH_2$. Haploinsufficiency elevates plasma proline levels by ~2-fold, producing hyperprolinemia that reaches cytosolic concentrations of ~5 mM in neurons (Liu et al., 2002; Crabtree et al., 2016).

At these concentrations, L-proline competitively inhibits glutamate decarboxylase (GAD; Ki = 7.8 mM), the enzyme responsible for GABA synthesis from glutamate (Jacquet et al., 2002). In $Prodh^{-/-}$ mice, this selectively impairs sustained high-frequency GABAergic transmission in prefrontal layer II/III, with enhanced IPSC depression at 33 Hz (p=0.038), mimicking GAD65-null phenotypes (Crabtree et al., 2016).

The effect is cell-type specific: localization to parvalbumin-positive (PV+) interneurons disrupts gamma oscillations (30-80 Hz), with severe impairment at 38 Hz (p=0.000174) - frequencies essential for cognitive control and working memory.

The genetic evidence supporting PRODH as a psychosis susceptibility gene is substantial. The PRODH2*1766/1945 2-2 haplotype shows significant transmission disequilibrium (P = 0.003), with carriers of pseudogene-like variants exhibiting 1.5-2-fold elevations in plasma proline (Liu et al., 2002). The Arg453->Cys substitution shows striking enrichment in childhood-onset schizophrenia (7.1% vs. 0.4% in controls, P = 0.015), while the Val427->Met variant appears in 16.6% of African American childhood-onset schizophrenia patients versus 1.3% of controls (P = 0.01). These variants cluster in exon 11 and map to conserved residues, suggesting functional impairment of enzymatic activity.

The PRODH-COMT epistatic interaction provides insight into dosage sensitivity and compensatory mechanisms. PRODH-deficient mice exhibit not only prepulse inhibition deficits but also upregulation of COMT, another deleted gene (Karayiorgou & Gogos, 2004). This suggests that proline accumulation triggers homeostatic responses in catecholamine metabolism, potentially explaining inconsistent COMT genotype associations with psychosis across studies.

The initial finding that COMTL hemizygotes showed greater prefrontal gray matter decline and cognitive deterioration (r = 0.71 between ΔVIQ and BPRS scores; Gothelf et al., 2005) failed to replicate in larger cohorts (Williams, 2011), likely because COMT effects are contingent on PRODH activity status and resultant proline levels.

Direct Measurement of E/I Imbalance

Proton magnetic resonance spectroscopy with MEGA-PRESS sequences provides direct in vivo measurement of neurotransmitter imbalance. Studies quantifying glutamate+glutamine (Glx) and GABA+ revealed elevated Glx in hippocampus and superior temporal cortex alongside reduced hippocampal GABA+ in 22q11.2 deletion carriers, indicating a shift toward excitatory predominance (Mancini et al., 2023).

Critically, deletion carriers with psychotic symptoms showed further Glx elevation in hippocampus, and longitudinal T1-weighted MRI revealed pronounced hippocampal volume loss inversely correlated with Glx levels ($r = -0.45$), supporting excitotoxicity as a degenerative mechanism.

The correlation between hippocampal Glx levels and lower full-scale IQ ($r = -0.38$) and aberrant resting-state functional connectivity suggests these cellular-level perturbations manifest as circuit-level dysfunction (Mancini et al., 2023). In Df(h22q11)/+ mice, hippocampus-to-medial prefrontal cortex (H-mPFC) long-term potentiation is abolished (137% vs. 195% potentiation in controls), with 29.6% fewer PV+ interneurons in mPFC layer 5/6 (Tripathi et al., 2020).

This PV+ deficit, independent of neuronal loss, arises from mitochondrial-ROS mediated apoptosis during maturation, impairing gamma oscillations essential for cognitive flexibility.

The hippocampal vulnerability to E/I imbalance reflects converging disruptions. First, parvalbumin interneuron dysfunction - driven by ATP deficits from MRPL40 haploinsufficiency - reduces GABAergic inhibition onto pyramidal neurons. Second, PRODH-mediated proline elevation impairs GAD-dependent GABA synthesis. Third, miR-223-mediated suppression of GRIN2B and GRIA2 alters glutamatergic receptor stoichiometry.

Fourth, excess glutamate triggers NMDA receptor overactivation, causing calcium influx and neuronal apoptosis via mitochondrial calcium overload - precisely the mechanism compromised by MRPL40 haploinsufficiency. This creates a vicious cycle: impaired mitochondrial calcium buffering exacerbates excitotoxicity, which further damages mitochondria, progressively degrading hippocampal function.

Stress Vulnerability and Circuit Decompensation

Stress vulnerability amplifies circuit dysfunction through glucocorticoid-mediated mechanisms. Df(h22q11)/+ mice show 42% higher corticosterone post-stress, abolishing LTP via glucocorticoid receptor hyperactivation (Tripathi et al., 2020). This effect is rescuable by clozapine (3 mg/kg) via D2 antagonism and PV+ stabilization, suggesting that antipsychotics may work partly by protecting vulnerable interneuron populations from stress-induced decompensation.

COMT haploinsufficiency adds stress sensitivity through altered catecholamine metabolism: the low-activity Met allele elevates sympathetic-adrenomedullary reactivity (salivary alpha-amylase, $p=0.026$, $\Delta=0.67$) without HPA axis cortisol changes, potentially synergizing with inflammation during adolescence (Beebe et al., 2024).

Blood-Brain Barrier Disruption: The Neuroimmune Interface

CLDN5 Haploinsufficiency and Structural Compromise

The deletion of CLDN5 (claudin-5), which encodes a tight junction protein expressed 100-fold higher than other claudins in brain endothelium, introduces a critical neuroimmune dimension. Blood-brain barrier-like endothelial cells derived from 22q11.2DS patients with schizophrenia exhibited significantly reduced transendothelial electrical resistance (TEER), indicating impaired barrier function (Crockett et al., 2021).

This was confirmed in Df(h22q11)/+ mice, which showed increased parenchymal extravasation of both IgG (150 kDa) and fibrinogen (340 kDa).

The molecular basis involves disrupted claudin-5 organization at tight junctions and reduced overall expression. Individuals carrying the CLDN5 rs10314 variant may express up to 75% less claudin-5 in the BBB, with postmortem studies revealing decreased CLDN5 protein despite elevated mRNA levels - attributed to protein kinase A-mediated phosphorylation promoting proteasomal degradation (Sukhorukova et al., 2025; Greene et al., 2018).

Beyond structural compromise, the BBB exhibits loss of immunoquiescence, with elevated ICAM-1 expression in patient-derived cells, mouse CNS vasculature, and human postmortem tissue (Crockett et al., 2021). This pro-inflammatory phenotype increases monocyte transmigration and reduces expression of the anti-inflammatory molecule thrombomodulin (CD141).

Mitochondrial-BBB Coupling

BBB endothelium possesses 2-3-fold higher mitochondrial density than peripheral vessels, reflecting the extraordinary ATP demands of active transport and tight junction maintenance (Oldendorf et al., 1977). In 22q11.2DS brain microvascular endothelial cells (iBMECs), ~20-30% reductions in basal oxygen consumption rate correlate directly with TEER decreases and claudin-5 disorganization (Crockett et al., 2025).

The specific deficits include: ~40% decrease in spare respiratory capacity, ~25% decrease in ATP-linked respiration, and ~30% elevation in reactive oxygen species without mtDNA copy number changes, pointing to fission/fusion imbalances (altered MFN1/MFN2 expression).

This creates a direct coupling between mitochondrial function and barrier integrity: reduced ATP availability impairs the energy-dependent processes maintaining tight junction protein localization and stability. Lipopolysaccharide challenge - mimicking infection - worsens oxygen consumption rate by an additional 20% and increases permeability by ~30%, highlighting gene-environment interactions (Crockett, 2023).

In 22qMc mice, BBB breach associates with perivascular astrogliosis, hippocampal IL-6 elevation (~2-fold), and social memory deficits. Remarkably, treatment with the PPARα agonist bezafibrate rescued these phenotypes: spare respiratory capacity increased 30%, TEER increased 15%, and MFN1/MFN2 expression increased 1.5-2-fold via PGC-1α-mediated enhancement of fusion/fission balance (Crockett et al., 2025).

Neuroinflammatory Consequences

Perivascular astrocytes show elevated GFAP expression and increased IL-6 production in both mouse models and human postmortem tissue, creating conditions for further neural damage (Crockett et al., 2021). Inflammatory cytokines can directly impair mitochondrial function, creating positive feedback with the primary MRPL40-driven bioenergetic deficit.

Moreover, BBB compromise allows peripheral immune cells and molecules into the CNS parenchyma, potentially triggering or exacerbating psychotic symptoms through immune-mediated mechanisms.

The demonstration that clozapine dose-dependently upregulates CLDN5 expression in brain microvascular endothelial cells (Greene et al., 2018) suggests that existing antipsychotics may work partly through barrier stabilization - a mechanism distinct from dopamine D2 receptor antagonism and potentially explaining why clozapine shows superior efficacy in treatment-resistant cases.

This finding opens therapeutic avenues for claudin-5 mimetics or other barrier-enhancing agents that could prevent psychosis onset rather than merely treating symptoms.

Immune Dysregulation: Th17 Skewing and Cytokine Imbalance

T-Cell Developmental Abnormalities

TBX1 haploinsufficiency causes thymic hypoplasia, resulting in partial T-cell immunodeficiency affecting up to 80% of 22q11.2DS individuals (Vergaelen et al., 2018). However, the simple reduction in T-cell numbers fails to explain psychosis risk; instead, the critical abnormality involves qualitative shifts in T-helper cell populations toward pro-inflammatory phenotypes.

Flow cytometric analysis reveals that 22q11.2DS individuals exhibit significantly elevated Th1 (CD3+CD4+IFN-γ+) and Th17 (CD3+CD4+IL-17+) cells, with Th17 elevation showing the strongest effect (partial $\eta^2 = 0.18$).

Within the 22q11.2DS cohort, Th17 percentage is significantly higher in individuals with psychotic symptoms compared to those without psychosis, controlling for antipsychotic medication (partial $\eta^2 = 0.13$), and correlates positively with PANSS positive symptom severity ($r=0.62$, $p<0.01$; partial $\eta^2 = 0.34$) (Vergaelen et al., 2018). This produces elevated Th1:Th2 and Th17:Treg ratios, indicating systemic pro-inflammatory imbalance that extends beyond simple T-cell deficiency.

Mechanisms of Neuroinflammatory Action

Th17 cells access the brain via the choroid plexus, delivering IL-17A-producing cells to regions near limbic structures. IL-17 receptors show widespread expression in neural tissue, and IL-17A modulates hippocampal neurogenesis and BDNF expression (Ozaki et al., 2021). In mouse models, myelin-reactive Th17 cells influence hippocampal neurogenesis, with deficiency reducing neurogenesis that is restored by adoptive transfer of Th17 populations.

This dual role - Th17 cells supporting physiological neurogenesis at homeostatic levels but producing pathology when overactivated - explains the complex relationship between immune activation and psychiatric symptoms.

Proteomic profiling of 22q11.2DS reveals elevated TNF, IL-6, MCP-3, CCL-19, IL-17C, TRAIL, IL-4, IL-33, and neurotrophins like GDNF, NT-3, and βNGF, forming a TNF-regulated inflammatory network (Frusone et al., 2024). This chronic inflammation compromises BBB integrity, allowing peripheral stressors to infiltrate neural circuits.

Cerebellar inflammation involving microglial activation and cytokine release - particularly TNF-α and ATP - induces intrinsic excitability plasticity in Purkinje cells, producing behavioral abnormalities including depression-like and autism-like phenotypes depending on the affected region (Ozaki et al., 2021).

Transcriptional Immune Signatures

RNA-Seq of lymphoblastoid cell lines from 22q11.2DS males with schizophrenia spectrum disorders reveals 48 differentially expressed genes (adjusted $p<0.05$), with 54% in immune-inflammatory response pathways and 85% downregulated (Michaelovsky et al., 2024). Downregulated genes include immunoglobulins, cytokines, and MHC class I molecules, while negative immune regulators (LILRB4, PXDN) are upregulated.

Ingenuity Pathway Analysis shows inhibited Th1/Th17 activation, natural killer signaling, and neuroinflammation (Z-score ≤ -2), with upstream regulators like IFNG, STAT1, and NFATC2 inhibited.

This paradoxical pattern - systemic Th17 elevation measured by flow cytometry but transcriptional suppression of immune pathways in lymphoblastoid lines - suggests complex regulatory dysfunction rather than simple activation.

Haploinsufficiency of CRKL, KLHL22, and USP41 (immune regulators within 22q11.2) likely initiates this dysregulation, compounded by endoplasmic reticulum stress from a 952-gene WGCNA module upregulated in schizophrenia spectrum disorders ($p=0.04$; $r=+0.49$), enriched for ER protein processing (FDR=$7.16\text{x}10^{-9}$) and N-glycan biosynthesis (FDR=0.04) (Michaelovsky et al., 2024).

This aligns with idiopathic schizophrenia ERAD/UPR dysregulation (Kim et al., 2018, 2019, 2021), where KLHL22/USP41 haploinsufficiency impairs ubiquitination/deubiquitination pathways, creating a "two-hit" proteostatic crisis.

Epigenetic Integration: The MHC Locus and Imprinted Genes

Genome-Wide Methylation Patterns

Genome-wide DNA methylation profiling comparing 22q11.2DS individuals with and without schizophrenia spectrum disorders reveals hypomethylation in genes regulating both immune function and genomic imprinting (Carmel et al., 2021). At stringent thresholds ($p < 10^{-6}$), 23 differentially methylated probes emerge, with all showing hypomethylation in the schizophrenia group.

The most significant finding involves the MHC locus on chromosome 6p21-22, which shows differential methylation encompassing both immune HLA genes (HLA-B,

HLA-DQB1) and non-immune genes with neurodevelopmental functions (RNF39, PPP1R18, NOTCH4).

The transcription regulator ZFP57, located within this region, represents a critical mechanistic node: it maintains imprinting and DNA methylation at multiple imprinting control regions, including SNRPN and GNAS, which themselves show differential methylation (Carmel et al., 2021). ZFP57 dysregulation has been independently implicated in both autism spectrum disorder and psychosis, suggesting it coordinates genomic imprinting across multiple loci.

ZFP57's role in protecting against TET-mediated demethylation during embryogenesis implies that DGCR8 haploinsufficiency indirectly disrupts imprinting via miRNA-targeted DNMTs, leading to sex-dependent neurobehavioral shifts (e.g., PEG10's paternal bias in serotonin receptor splicing).

Imprinted Gene Dysregulation

The enrichment of differentially methylated imprinted genes - including PEG10, SGCE, GNAS, GNAS-AS1, SNHG14, SNURF-SNRPN, and SNORD115 - indicates disruption of parent-of-origin-dependent gene regulation (Carmel et al., 2021). These genes regulate neurodevelopment, with the 15q11.2 cluster overlapping the Prader-Willi critical region and including small nuclear RNA genes involved in microglial activation and alternative splicing regulation of the 5-HT2C receptor.

The sex-dependent association of PEG10-SGCE imprinting control region methylation with neurobehavioral outcomes suggests these epigenetic alterations modulate neurodevelopmental trajectories in ways that interact with biological sex.

MHC differentially methylated regions (e.g., hypermethylated RNF39, NOTCH4, PPP1R18) link immunity to synaptic plasticity: RNF39 regulates LTP via HIPPO signaling; NOTCH4 modulates neural stem cell quiescence; PPP1R18 dephosphorylates PP1 in dendritic spines (Carmel et al., 2021). This immune-neuronal crosstalk, also seen in inter-chromosomal WGCNA modules (Lin et al., 2016), may exacerbate inflammation-driven synaptic pruning.

The detection of methylation signatures at birth that predict psychosis decades later demonstrates that vulnerability is established during neurodevelopment rather than emerging acutely at psychosis onset (Starnawska et al., 2017).

The enrichment of differentially methylated probes in neurogenesis pathways at birth suggests that the foundational architecture of psychosis risk is laid down prenatally and perinatally, with subsequent environmental exposures determining whether this vulnerable architecture decompensates.

Polygenic Modifiers and the Threshold Model

Second-Hit Genetic Architecture

The incomplete penetrance of psychosis in 22q11.2DS - only 25-40% despite uniform deletion - demonstrates that additional genetic factors determine outcome. Whole-exome sequencing identifies rare damaging variants in neurodevelopmental genes enriching pathways like neuron projection, cytoskeleton organization, histone modification, and olfactory transduction (Michaelovsky et al., 2019). Specific variants include ADCYAP1R1 rs61757359, GRM8 rs2237745, ACTR3B rs3742599, and KDM4B rs11137827.

These second hits appear to lower the threshold for psychotic decompensation by further compromising systems already stressed by the 22q11.2 deletion.

Schizophrenia polygenic risk scores (PRS) correlate with IQ decline and psychosis onset in 22q11.2DS, though 22q11.2DS-associated schizophrenia cases have lower PRS than idiopathic schizophrenia (R^2=0.04 vs. 0.12) (Monfeuga, 2017; Gur et al., 2021). This suggests the high-impact deletion reduces the additional polygenic burden needed to cross the psychosis threshold. Top-quintile PRS doubles conversion odds (OR=2.5), demonstrating additive effects between the deletion and common variants.

GWAS in ultra-high-risk cohorts identifies converters via upregulated synaptic/dopaminergic loci (e.g., NRXN1 rs1045881, DRD1 rs686, ARVCF rs165815 in 22q11.2), suggesting the deletion sensitizes individuals to variants in neurexin-adhesion and dopamine receptor signaling (Wang et al., 2024).

Deletion Size Effects and Genetic Background

Larger deletions (3 Mb vs. 1.5 Mb) worsen cognitive outcomes and increase psychosis risk, demonstrating gene dosage effects within the 22q11.2 region itself (Zhao et al., 2018; Sun et al., 2020). The 3 Mb deletion includes RANBP1 (RAN GTPase regulator) and additional genes that extend mitochondrial and synaptic deficits.

RANBP1 haploinsufficiency impairs nuclear transport of microtubule-associated proteins (e.g., MAP1A), leading to dosage-dependent cortical surface area reductions (d = -1.01), while smaller 1.5 Mb deletions (sparing RANBP1) preserve cortical surface area relative to 3 Mb variants (Sun et al., 2020).

Genetic background modulation provides crucial insight into incomplete penetrance. Sept5$^{-/-}$ mice show impaired social interaction on C57BL/6J backgrounds but not on 129S1-enriched backgrounds (Hiroi et al., 2012), demonstrating that modifier alleles elsewhere in the genome determine phenotypic expression.

Extrapolating to humans, the 25-40% psychosis penetrance likely reflects threshold effects where hemizygosity becomes pathogenic only when combined with specific polygenic backgrounds affecting synaptic function, stress response, or immune regulation.

Neurodevelopmental Trajectories and Critical Periods

Placental and Prenatal Origins

The pathophysiological cascade begins during prenatal development through effects on both placental and fetal brain tissues. Transcriptome-wide association studies of placental tissue highlight 262 schizophrenia-associated genes with placenta-specific expression quantitative trait loci, explaining ~16% of schizophrenia heritability - comparable to fetal brain eQTLs (~20%) (Birnbaum & Weinberger, 2024).

These genes, enriched in trophoblast cells, regulate cellular invasiveness, nutrient sensing, and oxygen homeostasis. In 22q11.2DS, deletion of genes like CRKL (involved in MAPK signaling for trophoblast differentiation) likely impairs placental function, leading to fetal hypoxia or nutrient deficits that bias second-trimester cortical development - a period of peak schizophrenia GWAS signal enrichment (postconception weeks 16-19).

Fetal growth and gestational factors predict schizophrenia outcomes: small for gestational age infants with 22q11.2DS show increased psychosis risk (Van et al., 2016). This suggests that early metabolic stress during gestation establishes vulnerability that persists through development, creating neural circuits with reduced resilience to subsequent challenges.

Childhood Cognitive Trajectories

Verbal IQ and language development decline precedes psychosis onset, with longitudinal studies showing 10-15 point IQ drops in individuals who later develop psychotic symptoms (Vorstman et al., 2015; Solot et al., 2020). Early language measures at ages 3-5 associate with later psychosis features, suggesting that neurodevelopmental perturbations manifest cognitively years before psychiatric symptoms emerge (Solot et al., 2020).

Executive function and social cognition impairments appear during childhood, with deficits in working memory, cognitive flexibility, and social processing predicting psychosis risk (Morrison et al., 2020).

Structural neuroimaging reveals progressive changes: cortical thinning accelerates in temporal and cingulate regions during adolescence in individuals who develop psychosis (Sun et al., 2018; Bagautdinova et al., 2021). This reflects excessive synaptic pruning driven by the combination of E/I imbalance, mitochondrial dysfunction, and oxidative stress-induced spine loss.

Craniofacial anomalies signal early midline disruptions that parallel forebrain and olfactory system dysgenesis, with olfactory deficits (Cohen's d=1.11) predicting negative symptoms independently of cognition (Tang et al., 2018; Moberg et al., 2020).

Adolescent Decompensation

Psychosis typically emerges in late adolescence or early adulthood, reflecting the convergence of three factors: completion of prefrontal cortex maturation with its attendant high metabolic demands, peak immune system challenges from infections and stress, and common environmental exposures like cannabis use. Individuals maintaining marginal compensation throughout childhood decompensate when these challenges simultaneously increase.

The neurodevelopmental timing of psychosis emergence reflects not merely social stress exposure but a fundamental vulnerability of maturing circuits undergoing activity-dependent refinement. Synapses with accumulated molecular deficits may function adequately under supportive developmental conditions but fail when pruning mechanisms - guided by altered activity patterns and compromised by oxidative stress - eliminate critical connections.

Adolescent synaptic pruning in prefrontal cortex normally refines circuits by eliminating approximately 50% of synapses; when E/I imbalance and mitochondrial dysfunction compromise the fidelity of this process, excessive elimination of functional connections produces the cognitive and perceptual abnormalities characteristic of psychosis.

Dopaminergic Dysregulation: The Final Common Pathway

Striatal Hyperdopaminergia from Upstream Perturbations

Despite diverse upstream perturbations, psychosis in 22q11.2DS converges on striatal dopaminergic dysregulation as a final common pathway. [18F]-DOPA PET imaging demonstrates elevated presynaptic striatal dopamine synthesis capacity in 22q11.2 deletion carriers with psychotic symptoms (Rogdaki et al., 2023). This hyperdopaminergia does not arise from isolated defects in dopamine metabolism but reflects multiple convergent mechanisms.

First, COMT haploinsufficiency reduces catechol-O-methyltransferase activity, impairing dopamine degradation in prefrontal cortex and producing elevated dopamine levels. However, reduced COMT also generates fewer quinone metabolites that undergo redox cycling, potentially providing partial protection against oxidative stress - complicating simple interpretations of COMT's role (Karayiorgou & Gogos, 2004).

Second, hippocampal hyperexcitability - driven by E/I imbalance and parvalbumin interneuron dysfunction - produces aberrant output that dysregulates ventral tegmental area dopamine neuron firing. The hippocampus normally provides context-dependent gating of VTA activity; when hippocampal processing becomes unreliable due to glutamate excess and GABA deficiency, inappropriate dopamine release in striatum produces aberrant salience attribution - a core feature of psychotic experience.

Third, reduced prefrontal cortical thickness and disrupted prefrontal-striatal connectivity compromise top-down regulation of subcortical dopamine systems. The prefrontal cortex normally provides tonic inhibition of striatal dopamine release; when this regulatory control fails, striatal dopamine becomes dysregulated even without primary abnormalities in dopamine neurons themselves.

Fourth, mitochondrial dysfunction in dopaminergic terminals impairs dopamine transporter (DAT)-mediated reuptake, which requires substantial ATP. Reduced ATP availability slows dopamine clearance from the synaptic cleft, producing functional hyperdopaminergia even without increased release.

Fifth, elevated miR-338-3p suppression (due to DGCR8 haploinsufficiency) increases D2 receptor expression, enhancing dopaminergic signaling for a given level of dopamine release (Zinkstok et al., 2019). This receptor upregulation creates supersensitivity to dopamine that amplifies the effects of increased synthesis and reduced clearance.

Network-Level Manifestations

Deep neural network analysis of functional connectivity patterns achieves 93.8% accuracy in classifying 22q11.2DS individuals (Supekar et al., 2024). The most discriminating features involve altered connectivity within the salience network (anterior cingulate cortex, anterior insula) and between the salience network and default mode network.

These alterations reflect the integration of upstream perturbations: hippocampal dysfunction disrupts memory and context processing, prefrontal dysfunction impairs cognitive control, and aberrant dopaminergic signaling produces inappropriate activation of the salience network in response to neutral stimuli.

The convergence on salience network dysfunction explains the phenomenology of psychosis: neutral internal and external stimuli become invested with inappropriate significance, producing ideas of reference, paranoid ideation, and ultimately delusional beliefs as the individual attempts to make sense of aberrant salience experiences.

The functional brain signatures are robust and replicable across cohorts, demonstrating that 22q11.2DS produces consistent network-level abnormalities despite individual variation in penetrance.

Integration: A Systems-Level Model of Psychosis Emergence

The mechanistic architecture of psychosis in 22q11.2DS reveals a multi-hit threshold model. The deletion creates a state of coordinated vulnerability through:

1. Mitochondrial insufficiency: Reduced ATP production, impaired calcium handling, elevated oxidative stress, and failed mitophagy create cellular energetic vulnerability, particularly affecting high-demand neurons like parvalbumin interneurons and neurons with extensive axonal arborization.
2. Transcriptional dysregulation: DGCR8 haploinsufficiency produces global miRNA depletion that desynchronizes developmental timing, reduces neuronal output during critical periods, and alters neurotransmitter receptor expression, creating neurons with reduced connectivity potential and altered response properties.
3. E/I imbalance: PRODH-mediated proline elevation inhibits GABA synthesis, parvalbumin interneuron ATP deficiency reduces inhibitory transmission, and miR-223-mediated suppression of glutamate receptors alters excitatory signaling, producing net hyperexcitability particularly in hippocampus and prefrontal cortex.

4. BBB compromise: CLDN5 haploinsufficiency combined with endothelial mitochondrial dysfunction produces structural barrier failure, allowing peripheral immune molecules and cells access to CNS parenchyma and creating conditions for neuroinflammation.
5. Immune dysregulation: TBX1-mediated thymic hypoplasia produces Th17 skewing and pro-inflammatory cytokine profiles that access the brain through compromised BBB, directly affecting neurogenesis, synaptic function, and circuit excitability.
6. Epigenetic instability: Altered methylation at imprinted genes and MHC loci creates parent-of-origin and sex-dependent variation in neurodevelopmental trajectories, modulating the expression of the deletion's effects.
7. Polygenic modification: Common and rare variants outside the deletion region determine whether compensatory mechanisms succeed or fail, explaining why only 25-40% of deletion carriers develop psychosis despite uniform genetic lesions.

These perturbations do not produce psychosis independently; rather, psychosis emerges when compensatory mechanisms fail to maintain homeostasis across these interconnected systems during adolescent neurodevelopment.

Non-psychotic deletion carriers successfully engage compensatory mitochondrial biogenesis, maintain lysosomal pH for effective mitophagy, preserve BBB integrity through alternative tight junction proteins, and recruit alternative neural circuits to compensate for hippocampal-prefrontal dysfunction. Psychotic individuals exhibit frank decompensation across all domains, suggesting that psychosis requires simultaneous failure across multiple systems rather than catastrophic failure of any single pathway.

Implications for Understanding Idiopathic Psychosis

Psychosis as a Neurodevelopmental Systems Disorder

The 22q11.2DS model reframes idiopathic psychosis as a neurodevelopmental disorder rooted in systems-level failures of mitochondrial resilience, immune homeostasis, and cellular quality control. This framework extends beyond rare CNVs to explain polygenic schizophrenia: rather than each GWAS locus independently conferring risk, common variants likely affect the same convergent pathways illuminated by 22q11.2DS - mitochondrial function, synaptic architecture, immune regulation, and developmental timing.

Postmortem schizophrenia brains show analogous mitochondrial deficits: 40% reduced anterior cingulate volume, downregulated OXPHOS genes, reduced mtDNA copy number ($p<10^{-40}$), and increased mtDNA mutations (Hjelm et al., 2015). iPSC models from idiopathic schizophrenia patients replicate membrane potential reductions and ROS excess predating spine loss, akin to 22q11.2DS (Hjelm et al., 2015). This suggests bioenergetic failure as a universal bottleneck regardless of genetic etiology.

The enrichment of schizophrenia GWAS signals in pathways dysregulated in 22q11.2DS - synaptic function, mitochondrial metabolism, immune signaling - indicates that distributed common variants affecting these pathways can phenocopy the concentrated haploinsufficiency of 22q11.2 deletion when polygenic burden exceeds threshold.

This explains the genetic architecture of schizophrenia: hundreds of common variants each slightly perturbing these systems, with clinical psychosis emerging when cumulative perturbations overwhelm compensatory capacity.

Cell-Type Vulnerabilities and Circuit Selectivity

The model highlights cell-type-specific vulnerabilities that explain circuit selectivity in psychosis. Parvalbumin interneurons, with their extraordinarily high metabolic demands due to rapid-spiking physiology and extensive axonal arborization, show preferential vulnerability to ATP deficits from MRPL40 haploinsufficiency (Devaraju & Zakharenko, 2017).

Their dysfunction explains why E/I imbalance emerges despite distributed genetic effects, and parallels observations in idiopathic schizophrenia showing parvalbumin interneuron deficits in postmortem studies.

Similarly, hippocampal pyramidal neurons - with their extensive dendritic trees and high baseline excitatory drive - become vulnerable to excitotoxicity when glutamate elevation combines with impaired mitochondrial calcium buffering. The regional specificity (hippocampus, anterior cingulate, prefrontal cortex) reflects not differential gene expression of 22q11.2 genes, but differential cellular vulnerability based on metabolic demands and network position.

Developmental Windows and Therapeutic Implications

The neurodevelopmental trajectory - with early cognitive deficits, adolescent prodromal features, and adult-onset psychosis - reflects progressive failure of compensatory mechanisms. Early mitochondrial dysfunction and white matter abnormalities create vulnerabilities that remain subclinical until adolescent synaptic pruning, hormonal changes, and increased metabolic demands overwhelm remaining reserves.

This suggests therapeutic windows: interventions targeting mitochondrial function, neuroinflammation, or BBB integrity during childhood could prevent psychosis onset rather than merely treating symptoms.

The rescue of cellular phenotypes through lysosomal pH normalization (Stronati et al., 2024) and behavioral phenotypes through bezafibrate-mediated mitochondrial biogenesis enhancement (Crockett et al., 2025) demonstrates that even established deficits remain plastic and responsive to intervention. This provides hope for disease-modifying treatments rather than purely symptomatic management.

The demonstration that IGF2 restoration rescues psychiatric phenotypes in Dgcr8+/- mice (Qin et al., 2020) provides proof-of-principle for mechanism-based interventions targeting specific molecular pathways.

Other potential interventions include: NAD+ precursors to support mitochondrial metabolism; mitochondrial-targeted antioxidants to reduce oxidative stress; claudin-5 mimetics or PPARα agonists to restore BBB integrity; anti-inflammatory agents targeting Th17 or specific cytokines; and compounds enhancing mitophagy or autophagy to improve cellular quality control.

The MHC Locus: A Convergent Hub

The prominence of the MHC locus in both 22q11.2DS methylation studies and general schizophrenia GWAS indicates that immune regulation represents a shared mechanism across genetic and sporadic psychosis. The MHC region consistently emerges as the most significant genetic locus in large-scale schizophrenia studies (Ermakov et al., 2022), with the complement component C4 showing structural variation strongly associated with schizophrenia risk (Sekar et al., 2016).

Increased C4 expression drives excessive synaptic pruning during adolescence, providing a direct mechanism linking immune molecules to circuit refinement abnormalities.

Approximately 30-50% of schizophrenia patients exhibit high inflammatory subtypes characterized by elevated IL-6, TNF-α, and IL-1β (Ermakov et al., 2022). This suggests immune-mediated psychosis may constitute a substantial subgroup amenable to targeted anti-inflammatory interventions. The fact that 22q11.2DS produces similar inflammatory signatures through TBX1-mediated thymic hypoplasia suggests diverse etiologies can converge on immune dysfunction as a core pathophysiological mechanism.

Incomplete Penetrance as a General Principle

The differential outcomes in 22q11.2DS - identical deletions producing heterogeneous phenotypes - demonstrates that genetic determinism is insufficient for psychiatric prediction. Even with identified genetic causes, outcomes remain probabilistic and context-dependent. Modifier genes, environmental exposures, developmental timing, sex, and stochastic processes collectively determine phenotypes.

This has profound implications for precision psychiatry: genetic risk stratification must incorporate measures of cellular resilience (oxidative stress response capacity), immune status (Th17:Treg ratios), cognitive trajectories (verbal IQ trends), and environmental exposures (infections, stress, substance use) to meaningfully predict and prevent psychotic outcomes.

The fact that non-psychotic 22q11.2DS individuals successfully compensate through enhanced mitochondrial biogenesis suggests that resilience factors - genetic or acquired - may be as important as risk factors. Understanding what enables successful compensation could identify therapeutic targets for enhancing resilience in high-risk individuals, shifting the field from deficit-focused to capacity-building approaches.

Conclusion

The 22q11.2 deletion syndrome illuminates psychosis as an emergent property of failed homeostatic compensation across interconnected biological systems. The deletion does not deterministically cause psychosis; rather, it creates a developmentally unstable neurobiological landscape where mitochondrial dysfunction, transcriptional dysregulation, E/I imbalance, BBB compromise, and immune dysregulation synergistically erode the resilience of hippocampal-prefrontal and salience circuits.

Psychosis manifests specifically in individuals who fail to engage compensatory mitochondrial biogenesis, maintain cellular quality control through effective mitophagy,

preserve BBB integrity, and regulate immune responses - usually in the context of additional genetic variants or environmental stressors during critical developmental windows.

This framework explains psychosis more broadly as a threshold disorder where diverse genetic and environmental perturbations affecting mitochondrial function, synaptic architecture, immune regulation, and developmental timing can produce similar clinical outcomes through convergent pathways.

The 22q11.2DS model provides a mechanistic blueprint applicable across the schizophrenia spectrum, identifying specific molecular targets for intervention: mitochondrial metabolism, lysosomal function, BBB integrity, Th17 activation, and synaptic E/I balance.

Perhaps most importantly, it demonstrates that cellular and circuit-level abnormalities remain plastic and potentially reversible even after symptom onset, offering genuine hope for disease-modifying treatments that alter trajectories rather than merely suppressing symptoms.

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