脑铁沉积性神经变性病（NBIA）：概览

NBIA 是一组罕见、遗传性、进行性神经变性综合征，核心特点是基底节等部位出现**异常铁沉积**，并伴随复杂运动障碍和认知/精神症状。近年来多种致病基因被发现，使这一疾病群的遗传学与分型逐渐清晰，但发病机制和根本治疗仍未解决。

疾病定义与流行病学

- NBIA 代表一组以脑内铁沉积、尤其是苍白球和黑质为特征的进行性神经变性病，常见表现包括肌张力障碍、帕金森综合征样症状、舞蹈样动作、痉挛、言语障碍、智力低下和行为异常等 (Wiethoff & Houlden, 2017; Hayflick et al., 2018; Schneider, 2016; Meyer et al., 2015; Wiśniewska et al., 2025; Kruer et al., 2012; Arber et al., 2015)。
- 总体发病率约 2–3/100 万，多为遗传性单基因病，年龄起病从婴儿期到成人期不等 (Hajati et al., 2021; Schneider, 2016; Wiśniewska et al., 2025; Iankova et al., 2021)。

主要 NBIA 亚型与基因

亚型/类别	主要致病基因/通路	简要临床特征	引文
PKAN	PANK2，CoA 代谢	多为儿童起病、严重肌张力障碍	(Schneider, 2016; Hinarejos et al., 2020; Meyer et al., 2015; Kruer et al., 2012)
PLAN	PLA2G6，脂质/磷脂代谢	婴儿或儿童神经轴索营养不良，痉挛+认知退化	(Hayflick et al., 2018; Hajati et al., 2021; Meyer et al., 2015; Arber et al., 2015)
MPAN	C19orf12，线粒体/脂代谢	进行性锥体外系+痉挛	(Hajati et al., 2021; Schneider, 2016; Hinarejos et al., 2020; Mertiri et al., 2025)
BPAN	WDR45，自噬	静止性脑病+成人期进行性神经变性	(Schneider, 2016; Hinarejos et al., 2020; Svetel et al., 2021; Mertiri et al., 2025)
铁代谢直接异常	FTL1（神经铁蛋白病）、CP（无铜蓝蛋白血症）	多为成人起病运动障碍、认知障碍	(Hogarth, 2015; Hayflick et al., 2018; Svetel et al., 2021; Schneider et al., 2012)

Figure 1: 主要 NBIA 类型的基因及临床轮廓

遗传学与分型特点

- 目前已确定约 14–16 个 NBIA 相关基因，大多数为**常染色体隐性**，也有常染色体显性（如 FTL1）和 X 连锁显性（WDR45）等 (Hogarth, 2015; Gregory et al., 2008; Hinarejos et al., 2020; Wiśniewska et al., 2025; Di Meo & Tiranti, 2018; Schneider et al., 2012)。
- 只有少数基因（FTL、CP）直接参与铁代谢，多数基因涉及**脂质代谢、CoA 合成、线粒体功能、自噬/溶酶体途径**等，提示铁沉积多为这些通路失衡的“终末表型”之一 (Hogarth, 2015; Gregory et al., 2008; Hajati et al., 2021; Hinarejos et al., 2020; Schneider et al., 2012; Mertiri et al., 2025)。
- 约 65–85%的 NBIA 患者可找到已知基因突变，其余病例提示仍有未知基因存在 (Schneider, 2016; Hinarejos et al., 2020; Kruer et al., 2012; Marupudi & Xiong, 2024)。

病理与发病机制要点

- 影像与病理：T2 或 T2*加权 MRI 在基底节对称性低信号提示铁沉积，部分亚型出现特征性“虎眼征”；神经病理上可见基底节局灶性铁积聚、广泛轴索球样膨大，部分病例伴 Lewy 小体、tau 或 TDP-43 蛋白病理 (Wiethoff & Houlden, 2017; Hajati et al., 2021; Schneider, 2016; Meyer et al., 2015; Svetel et al., 2021; Schneider et al., 2012)。
- 共同机制：
    - **线粒体功能障碍与氧化应激**在多种亚型中被强调 (Hajati et al., 2021; Hinarejos et al., 2020; Schneider et al., 2012; Mertiri et al., 2025)。
    - 脂质代谢和膜稳态受损、自噬/溶酶体异常与铁稳态紊乱相互交织，引发神经元退行性改变和可能的铁依赖性细胞死亡（类似铁死亡） (Hajati et al., 2021; Hinarejos et al., 2020; Schneider et al., 2012; Mertiri et al., 2025; Kurian et al., 2011)。
    - 对于多数亚型，铁沉积是**因果还是结果**仍存在争议 (Hogarth, 2015; Hajati et al., 2021; Mertiri et al., 2025)。

临床表现、诊断与治疗进展

- **临床谱系**：从婴儿期快速全面退化，到成人期轻-中度帕金森综合征，常伴认知退化、精神症状、视网膜或外周神经受累等，表型高度异质且不同亚型间有重叠 (Wiethoff & Houlden, 2017; Hayflick et al., 2018; Schneider, 2016; Meyer et al., 2015; Kruer et al., 2012; Arber et al., 2015; Marupudi & Xiong, 2024)。
- **诊断策略**：
    - 结合进展性运动障碍+基底节铁沉积 MRI 改变，提示 NBIA (Hayflick et al., 2018; Schneider, 2016; Meyer et al., 2015; Svetel et al., 2021)。
    - 现多采用**基因 Panel 或全外显子测序**进行分子确诊，并逐步发现新的致病基因 (Gregory et al., 2008; Schneider, 2016; Hinarejos et al., 2020; Meyer et al., 2015; Wiśniewska et al., 2025)。

- **治疗现状与探索：**
    - 目前以对症治疗（肌张力障碍、痉挛、精神症状等）为主，预后多为进行性恶化 (Wiethoff & Houlden, 2017; Hayflick et al., 2018; Wiśniewska et al., 2025; Kruer et al., 2012; Arber et al., 2015; Di Meo & Tiranti, 2018; Iankova et al., 2021)。
    - 铁螯合剂如去铁酮能够减少基底节铁负荷，在 PKAN 有放射学改善及疾病进展减缓趋势，但临床效果有限且个体差异大 (Wang & Jiang, 2021; Levi & Tiranti, 2019; Mertiri et al., 2025)。
    - 针对特定通路的“机制性”干预正在探索：替代底物（如 fosmetpantotenate、4'-phosphopantetheine）、激活其他同工酶（PZ-2891）、抗脂质过氧化（D-PUFA）、利用旧药（如去甲丙咪嗪）调控下游代谢，以及**基因替代治疗**的前临床研究 (Wang & Jiang, 2021; Levi & Tiranti, 2019; Iankova et al., 2021)。

NBIA 是一大类以基底节异常铁沉积为共同特征的单基因神经变性病，临床表现复杂多样、起病年龄跨度大。致病基因主要指向 CoA 和脂质代谢、线粒体功能与自噬等通路，铁沉积更像多种细胞过程失败后的“交汇点”。目前尚无公认的根本治疗，铁螯合和针对特定代谢缺陷的精准干预处在探索阶段，更深入理解基因—通路—铁稳态之间的关系，是未来开发有效疾病修饰治疗的关键。

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