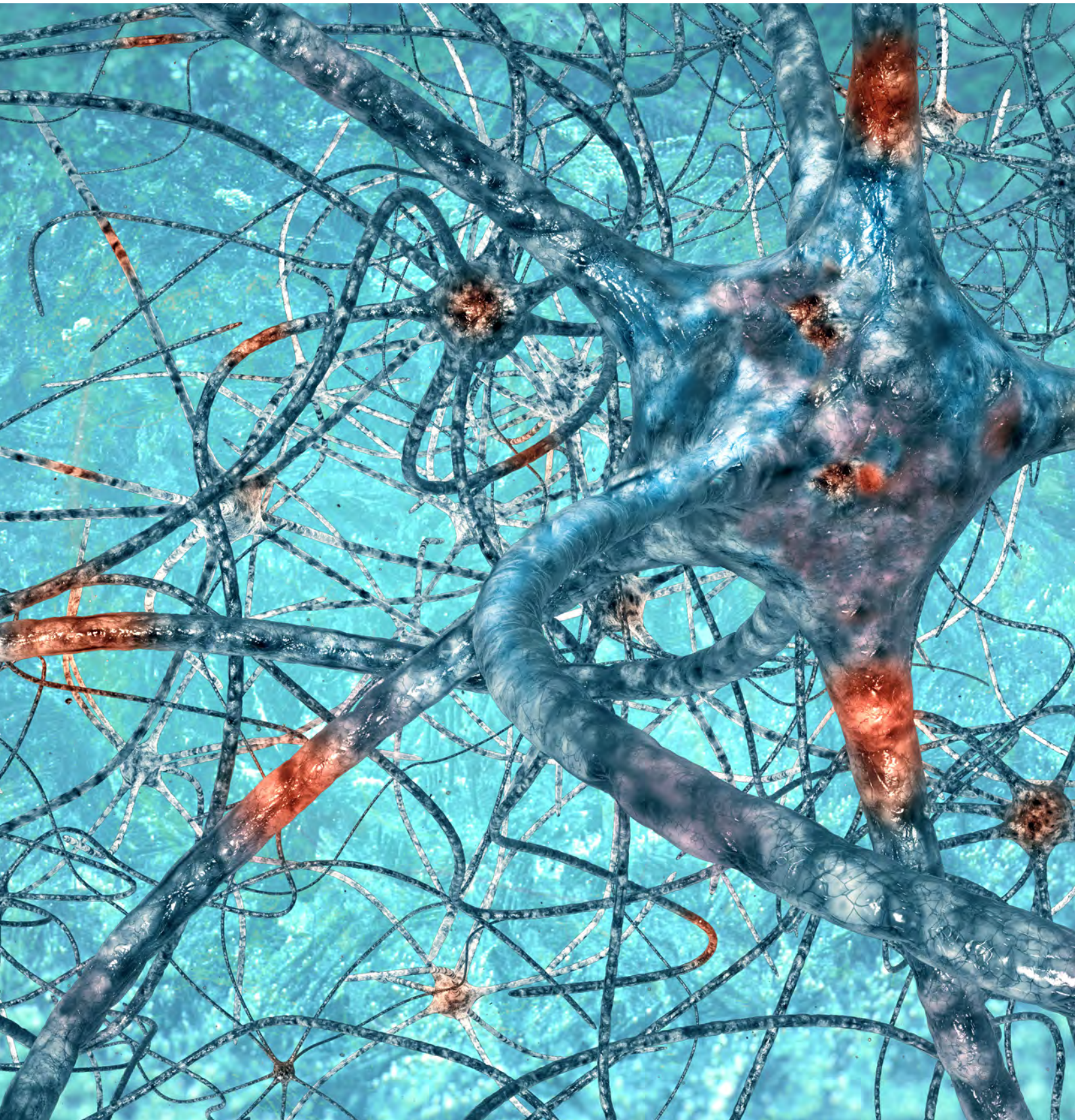
神经生物学研究综述

近期以Illumina技术为特色的文献综述

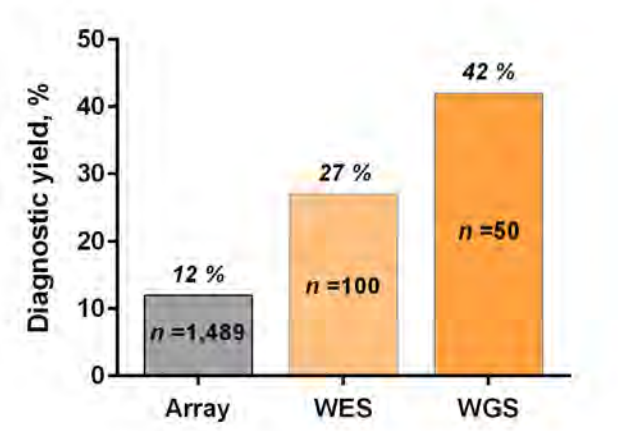


目录

简介

神经系统疾病是由遗传、环境和生活方式因素共同引起的复杂疾病。大多数神经系统疾病，如精神分裂症、自闭症、阿茨海默病和帕金森病，在几十年前就已有描述。不过，直到最近通过新一代测序（NGS）的使用，它们的全面复杂性才得以被揭开。[1,2]人们逐渐意识到，疾病发展是通过体细胞（非遗传）突变、遗传突变和表观遗传修饰的复杂相互作用来驱动的。[3,4,5,6]这种复杂性导致基因型与表型的关联非常弱，相同的疾病可能在不同个体上呈现出各种各样的病理表型。当然，不同的神经系统疾病表现出类似的症状（如痴呆，譬如帕金森病和路易体痴呆），也就不足为奇了。[7]这些重叠的症状可能表明有相同的内在分子机制参与。建立在这些内在分子过程以及所观察到的表型之基础上的诊断，有望在未来实现更加客观和准确的诊断和治疗。[8]

从NGS中获得越来越多的信息以及各种文库制备的方法为揭示精神病学的、神经退行性疾病的基因组和表观基因组领域带来了十分可观的设备工具。不断深入的认识最终将推动新型有效疗法的开发。此外，全基因组测序（WGS）有望检测这些疾病的倾向（易感性），实现预防保健和早期干预。最近宣布的由Genomics England发起的大型十万人基因组计划，表明了基因组诊断对未来医学的重要性。



严重智力障碍（IQ＜50）患者的诊断率，具体到各项技术：基因组芯片、全外显子组测序（WES）和WGS。百分比表示利用指定技术确定患病原因的患者数量。[9]

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疾病

神经系统疾病代表了一系列让人望而生畏的复杂多因素病理异常，范围可从轻微异常到致命异常。为了阐明最新的研究和基因组学的使用，本综述以精神分裂症和自闭症作为复杂神经发育疾病的例子，以阿茨海默病和帕金森病作为神经退行性疾病的例子。在这些研究中所采用的方法和技术可应用到广泛的神经系统疾病中。

精神分裂症

精神分裂症是最复杂的精神疾病之一，全球高达1%的成年人受此病影响。[10]最常见的症状包括非理性思维、幻听、错误信念和社会活动减少。疾病通常在12至25年时间内发展，是一种遗传性很高的多基因疾病。最近的基因组分析研究表明，精神分裂症可归因于一千多个基因位点，其中许多出现在基因组的非编码部分。[11-15]相当一部分的精神分裂症风险等位基因也与这个诊断类别中的其他疾病有关联，如双相障碍、自闭症和抑郁症。[16,17,18]所有这些疾病都是真正的谱系疾病，对其遗传原因和靶向疗法的开发有复杂的认识。然而，高通量基因测序技术的进步为更深入地分析这些疾病的遗传基础提供了有力工具，也为揭开多种遗传和表观遗传修饰的复杂相互作用带来了希望。

在精神分裂症中，基因型与表型的关联是非常弱的，同一种疾病可能在不同患者身上出现多种病理的表型。对双胞胎的研究发现，关于形成精神分裂症的风险，80%以上来自遗传倾向性，但环境风险因素的暴露也可能发挥重要作用。[20]在精神分裂症中检测到的第一批遗传突变是稀有变异，包括拷贝数变异（CNV）。[21]总体来说，这些变异约占到病例疾病的20%。[22]剩下的遗传病例最有可能是常见变异。[23]根据推测，个体常见变异的影响是轻微的；不过，共同作用之下它们可能也足以引发精神分裂症。[24,25]

> “精神分裂症的倾向性正被定位到数百个基因位点，也许最终超过一千个，每个都带来小增量的风险。” Hyman 2014

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遗传分析除了能确定导致精神分裂症的个体突变，它还有望为其他一些重要问题带来答案，比如为什么精神分裂症的发展与加速衰老相关联，[26]以及为什么精神分裂症患者在年轻时受心脏病、肺部疾病和代谢疾病折磨的比率要比一般人群高得多[29]。这些影响可能源于其他的生活方式风险，如药物滥用或吸烟。大约50%的慢性精神分裂症患者有着药物滥用的问题，他们发展成该疾病的风险比一般人群高4.6倍。在美国，超过80%的精神分裂症患者也是老烟枪，[30]因为尼古丁作为尼古丁乙酰胆碱受体的激动剂，有可能减缓与精神分裂症相关的一些认知损害。[31]

在精神分裂症患者中，吸烟和药物滥用很常见。在美国，超过80%的精神分裂症患者是老烟枪，[32]因为尼古丁可能减缓与精神分裂症相关的一些认知损害。

对疾病的潜在分子机制进行早期、准确且客观的诊断将有助于通过现有疗法更好地控制这种疾病。在较长远的未来，改善对疾病的认识将帮助人们开发出更有效、靶向且个性化的疗法。

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在精神分裂症的已知风险等位基因中，唯一明确增加风险的因素是染色体CNV，它们涉及到数千个DNA碱基的缺失或重复。此研究调查了小的新发突变的影响，它们影响一个或几个核苷酸。利用Illumina HiSeq对623个精神分裂症家系进行WES测序，作者评估了新发突变率以及精神分裂症、智力障碍和自闭类障碍（ASD）的共同遗传病因。他们获得了一些线索，表明病因机制有共同之处。

Illumina的技术：HiSeq用于外显子组测序

Karayannis T., Au E., Patel J. C., Kruglikov I., Markx S., et al. (2014) Cntnap4 differentially contributes to GABAergic and dopaminergic synaptic transmission. Nature 511: 236-240
为了了解神经系统疾病的发展，人们以神经细胞中表达的蛋白质为背景，研究了遗传影响。在这项研究中，作者鉴定了CNTNAP4敲除对小鼠行为和发育的影响，并将这些结果与人类CNTNAP2基因所在区域的CNV相关联。作者发现，CNTNAP4位于突触前，而它的损失导致皮层小清蛋白（PV）阳性的氨基丁酸能篮状细胞的产量减少。此外，CNTNAP4突变小鼠表现出这些神经群体的缺陷，以及感知运动门控和修饰的内表型。

Illumina的技术：HumanHap550，HumanOmni1-Quad

Purcell S. M., Moran J. L., Fromer M., Ruderfer D., Solovieff N., et al. (2014) A polygenic burden of rare disruptive mutations in schizophrenia. Nature 506: 185-190
鉴定复杂遗传病的基因关联仍然颇具挑战性，而样本量少是发现显著影响的一大障碍。在这项精神分裂症研究中，作者采用Illumina的技术对2,536个精神分裂症病例和2,543个对照开展WES。他们发现破坏性的突变分布在许多基因中；然而，经过多次检测校正，没有一个针对低频率和比较大影响的基因检测具有显著性。

Illumina的技术：HiSeq 2000，Genome Analyzer*IIx*

Schizophrenia Working Group of the Psychiatric Genomics C. (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511: 421-427
精神分裂症是一种遗传性很高的疾病，但遗传可能性不表现为单基因效应。在这个迄今为止最大型的精神分裂症全基因组关联研究（GWAS）中，作者利用单核苷酸多态性（SNP）芯片来分析36989个病例和113075个对照以确定疾病的遗传风险因素。他们发现明显的遗传关联并不是随机分布在基因组中，而是集中在大脑表达的基因以及与典型的共病诊断（如ASD和智力障碍）相关联的基因。有意思的是，关联也集中在与免疫力相关的基因，这符合精神分裂症存在免疫失调的假说。

Illumina的技术：Human1M，HumanOmni2.5，HumanOmniExpress，HumanHap550，Human610，HumanHap650Y，HumanHap300

Stefansson H., Meyer-Lindenberg A., Steinberg S., Magnusdottir B., Morgen K., et al. (2014) CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505: 361-366
某些CNV促成了精神分裂症和自闭症的发病。在这项研究中，作者调查了这些CNV对与上述疾病分离的表型的影响。在一项涉及到近三分之一冰岛人群的大型群体研究中（n = 101655），作者利用Illumina的SNP芯片来检验CNV与认知障碍、诵读困难、计算困难和大脑结构改变的关联。他们发现，15q11.2（BP1-BP2）的缺失影响了大脑结构，其模式与精神分裂症和诵读困难的首发精神病一致。

Illumina的技术：HumanHap300，HumanCNV370-Duo，HumanHap650Y，Human1M，HumanOmni2.5，HumanOmniExpress，HumanOmni1S

Yoon K. J., Nguyen H. N., Ursini G., Zhang F., Kim N. S., et al. (2014) Modeling a genetic risk for schizophrenia in iPSCs and mice reveals neural stem cell deficits associated with adherens junctions and polarity. Cell Stem Cell 15: 79-91

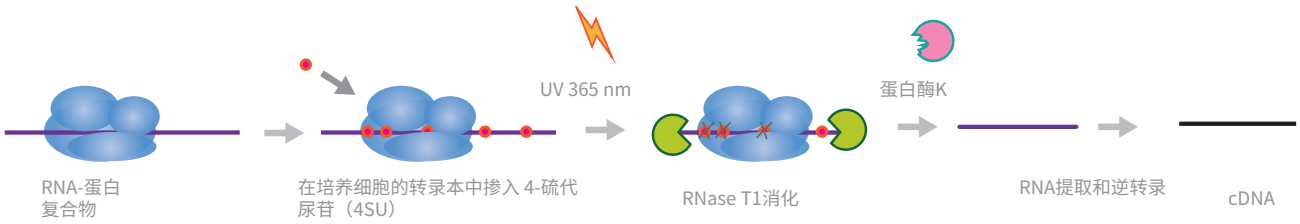
大脑发育的缺陷可能导致神经精神疾病的发生。这项研究试图确定15q11.2缺失对神经发育的功能作用，作者利用RNA-Seq和SNP基因分型芯片，研究了诱导多能干细胞（iPSC）来源的人神经前体细胞（hNPC）。他们发现15q11.2中的一个基因CYFIP1的单倍型不足影响了放射状胶质细胞，导致它们在脑室区外的定位异常。

Illumina的技术：HumanOmni2.5S

Stoll G., Pietilainen O. P., Linder B., Suvisaari J., Brosi C., et al. (2013) Deletion of TOP3beta, a component of FMRP-containing mRNPs, contributes to neurodevelopmental disorders. Nat Neurosci 16: 1228-1237

包括mRNA结合蛋白在内的遗传研究为mRNA代谢与疾病的关联带来了新的见解。在这项研究中，作者发现TOP3b基因的缺失与芬兰北部人群的神经发育疾病存在关联。他们将基因分型与可光活性增强的核糖核苷交联和免疫沉淀（PAR-CLIP）相结合，发现胞浆信使核糖核蛋白（mRNP）对TOP3b的召集与FMRP的共召集相偶联，而后者是与脆性X综合征相关的疾病基因。

Illumina的技术：Human Gene Expression，Human610-Quad，HumanHap330，HumanCNV370-Duo



光活性增强的核糖核苷交联和免疫沉淀（PAR-CLIP）可定位RNA结合蛋白（RBP）。[33]这种方法与交联免疫沉淀结合高通量测序（HITS-CLIP）和交联免疫沉淀测序（CLIP-Seq）类似，不过采用更有效的交联来稳定蛋白-RNA复合物。因为反应需要光激活的核糖核苷，因而限制了这种方法在细胞培养物和体外系统中的使用。在这一方法中，4-硫代尿苷（4-SU）和6-硫代鸟苷（6-SG）被掺入培养细胞的转录本中。紫外照射让4-SU/6-SG标记的转录本与相互作用的RBP交联。对靶向复合物进行免疫沉淀，利用RNase T1消化，接着进行蛋白酶K处理，以及RNA提取。将RNA逆转录成cDNA并测序。对cDNA的深度测序准确定位了与标记转录本相互作用的RBP。（更多方法请看：http://applications.illumina.com/applications/sequencing/NGS-library-prep/library-prep-methods.ilmn）

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自闭症谱系障碍

自闭症谱系障碍（ASD）包含一组多基因、多位点的疾病，[34]往往伴随着其他疾病的症状，如发育障碍/智力障碍（DD/ID；超过ASD病例的40%）、注意力缺陷/多动症（ADHD；59%–75%）、强迫症（OCD；60%）、癫痫（7%–46%）以及其他的神经和行为模式。[35,36]自闭症的发病率正在迅速增加，从2000年的0.7%增长到2010年的1.1%。[37]在美国，每68名儿童中就有一名被诊断出患有自闭症。这种趋势的部分原因在于对疾病诊断手段的提高。人们对ASD遗传成因的认识不断改善有望促进姑息疗法或治疗护理方案的开发。同时，这也有助于提供一种更准确的方法，来评估风险群体的精神状况，如罪犯及患有其他精神疾病的个体。[38,39,40]

自闭症主要是一种遗传性疾病，自闭症儿童的兄弟姐妹患上疾病的风险要高15–30倍。[41]据估计，这种疾病的遗传可能性高达90%–96%，说明非遗传因素仍未确定。[42,43,44]目前仍需要一种更准确的系统方法来改善典型自闭症和复杂（综合征、散发）自闭症的区分（表1）。基因组方法有望成为能区分不同种类的自闭症[45]的有效且可靠的工具。

表1：自闭症的类型

疾病类型	病例百分比	疾病特点
典型自闭症[46]	75%	男性的比例高于女性 缺乏畸形特征 兄弟姐妹复发风险高 家族史呈阳性 常见的基因变异
复杂（综合征、散发）自闭症[47]	25%	大量的高度外显罕见突变

与精神分裂症相似，ASD也是一种异质性的疾病。[48]这种异质性不仅体现在个体上，还能在大脑的不同部位观察到。小鼠实验表明，基因表达可能随着分析时机的不同而改变。[49]

> “从现在起两年后，研究人员需要一件更大的T恤来彰显他们的成果。” Wright 2014

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46. Rosti R. O., Sadek A. A., Vaux K. K. and Gleeson J. G. (2014) The genetic landscape of autism spectrum disorders. Dev Med Child Neurol 56:12-18
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CNV是第一种与自闭症相关联的突变类型。[50,51]CNV的新发出现率比对照高3–7倍。受自闭症相关CNV影响最大的基因群是GTPase/Ras、泛素降解基因，以及参与突触发育、轴突靶向和神经元运动的基因。[52,53,54]5%–10%的ASD患者存在大的CNV，主要是有着综合征ASD表型的患者。[55,56,57]自闭症个体中的独有CNV也常常影响编码突触蛋白和神经细胞粘附蛋白的基因。[58]（详见拷贝数变异）

此外，ASD也可能由罕见的突变、缺失、重复[59]以及大的染色体异常引起，这些可能是遗传的，也可能是新发的。[60]目前已知单基因突变导致了2%–5%的综合征病例，而脆X染色体综合征、PTEN巨头症和结节性硬化是最常见的异常。[61,62]PTEN突变也与肿瘤综合征强烈相关。[63]

双胞胎研究已成为精神疾病研究的一个标准模型。利用他们，人们可评估基因和环境对疾病风险的贡献。

最近的WES和WGS研究已经鉴定出多个可信度高的ASD基因。[64]目前有两项大型的WGS项目，一个是由英国政府联合Illumina和惠康基金会（Wellcome Trust）发起的（十万人基因组计划），另一个是由华大基因研究院（BGI）联合自闭症之声（Autism Speaks）发起的（自闭症基因组10K计划）。后一项研究的试点结果已经由Jiang等人发表。[65]

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表观遗传学

ASD的易感性可发生在遗传和表观遗传水平。[66]一些研究小组已从自闭症个体的死后样本中独立鉴定出多个差异甲基化的区域（DMR）。这些生物学上多样的基因区域包括DNase超敏位点和选择性转录本终止位点。[66,67,68]这些研究为表观遗传学在复杂疾病（如ASD）中的作用增添了证据。

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尽管ASD已经被广泛研究，但遗传可能性的比例和性质仍然不清楚。这项研究分析了迄今为止最大的自闭症队列数据，包括160万个瑞典家庭（至少有两个孩子）和大约5700名经过严格的自闭症诊断的个体。利用Illumina的SNP芯片，作者研究了罕见和常见遗传变异对疾病的贡献。他们的结论是，遗传可能性约为52.4%，而常见变异是最大的贡献因素。罕见的新发突变对个体患病的贡献可观，但它们对倾向差异的贡献是中度的，约为2.6%。

Illumina的技术：OmniExpress和Exome

Lee H., Lin M. C., Kornblum H. I., Papazian D. M. and Nelson S. F. (2014) Exome sequencing identifies de novo gain of function missense mutation in KCND2 in identical twins with autism and seizures that slows potassium channel inactivation. Hum Mol Genet 23: 3481-3489

许多研究报告了自闭症和癫痫的共患病，但这两种疾病之间的关系还不清楚。在这项研究中，作者利用外显子组测序对同卵双胞胎进行研究，他们都患有自闭症和严重的顽固性癫痫。作者在双胞胎中观察到KCND2基因的一个新型变异。这个新发突变位于编码Kv4.2钾离子通道的蛋白质上，作者在爪蟾卵母细胞中表达了这个突变蛋白，以观察功能影响。表达分析表明，突变明显破坏了钾离子通道的关闭状态失活，有力支持了KCND2作为此家族癫痫的致病基因。

Illumina的技术：HiSeq 2000，Illumina的双端测序文库制备方案

King I. F., Yandava C. N., Mabb A. M., Hsiao J. S., Huang H. S., et al. (2013) Topoisomerases facilitate transcription of long genes linked to autism. Nature 501: 58-62

发育中的大脑和成人大脑中都表达拓扑异构酶，而一些ASD患者的这种酶发生突变。然而，拓扑异构酶通过哪种机制来影响ASD，目前还不清楚。作者利用转录组测序以及神经元中RNA聚合酶II密度的全基因组定位，发现在敲除神经元的拓扑异构酶后，长基因的表达下降。作者指出，许多可信度高的ASD候选基因都特别长，但在TOP1抑制后表达下降。这种现象表明，有缺陷的拓扑异构酶可能促进了ASD。

Illumina的技术：HiSeq 2000，TruSeq RNA，TruSeq，用于ChIP-Seq

Ladd-Acosta C., Hansen K. D., Briem E., Fallin M. D., Kaufmann W. E., et al. (2013) Common DNA methylation alterations in multiple brain regions in autism. Mol Psychiatry

遗传以及环境因素都是ASD的原因。在这项研究中，作者测定了19个自闭症病例的大脑组织中超过48.5万个CpG位点，鉴定出四个在全基因组范围明显不同的DMR。这项研究突出了一组新的受影响基因。

Illumina的技术：HumanMethylation450

Willsey A. J., Sanders S. J., Li M., Dong S., Tebbenkamp A. T., et al. (2013) Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell 155: 997-1007

近期的WES和WGS研究已经鉴定出九个可信度高的ASD基因。这项研究将Illumina的WES和RNA-Seq数据融合成共表达网络，研究了这九个基因对常见表型的贡献。作者解释了这些网络将如何指导未来的ASD研究，它们表明哪些基因最可能有重叠的分子、细胞或回路水平的表型。

Illumina的技术：HiSeq 2000，Genome Analyzer

Yu T. W., Chahrour M. H., Coulter M. E., Jiralerspong S., Okamura-Ikeda K., et al. (2013) Using whole-exome sequencing to identify inherited causes of autism. Neuron 77: 259-273

Steel综合征是一种发育的结构失调，1993年在波多黎各的23名西班牙裔儿童中首次发现。这篇论文介绍了对一个家庭的基因组分析，这个家庭有两个患病的兄弟姐妹。作者利用Baylor医学院人类基因组测序中心（BCM-HGSC）设计的全外显子组测序，对患病的儿童及其父母、另一个患病的表亲及其未患病的父母进行测序。通过分离来过滤检测到的遗传变异，作者发现了一个与疾病分离的纯合错义突变。这个变异破坏了胶原蛋白基因COL27A1，它编码软骨发育时表达的一种蛋白质。

Illumina的技术：HiSeq 2000，HumanOmniExpress

Lionel A. C., Tammimies K., Vaags A. K., Rosenfeld J. A., Ahn J. W., et al. (2014) Disruption of the ASTN2/TRIM32 locus at 9q33.1 is a risk factor in males for autism spectrum disorders, ADHD and other neurodevelopmental phenotypes. Hum Mol Genet 23: 2752-2768

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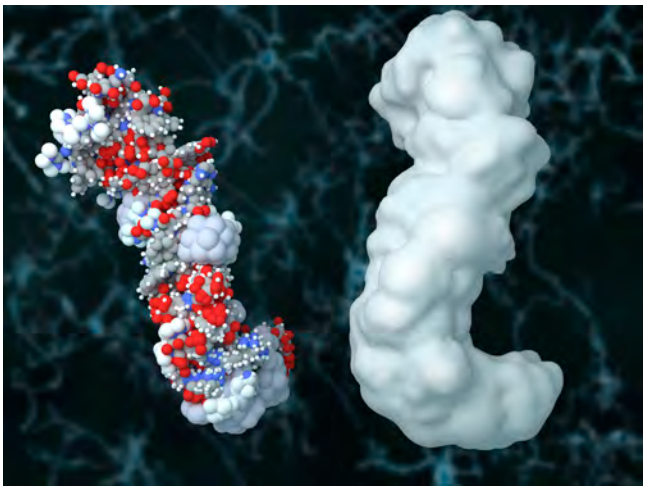
Nava C., Keren B., Mignot C., Rastetter A., Chantot-Bastaraud S., et al. (2014) Prospective diagnostic analysis of copy number variants using SNP microarrays in individuals with autism spectrum disorders. Eur J Hum Genet 22: 71-78

Wong C. C., Meaburn E. L., Ronald A., Price T. S., Jeffries A. R., et al. (2014) Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. Mol Psychiatry 19: 495-503

阿茨海默病

阿茨海默病(AD)是最常见的痴呆症形式，全球超过4000万人患有此病，到2050年，发病率可能翻一番。[70]在65岁及以上的人群中，11%的人患有这种致命的神经退行性疾病，而对于85岁及以上的人，发病率高达32%。[71]AD的早期症状包括记忆新信息的能力逐渐变差，[72]接着是混淆、易怒、语言有困难，以及长期记忆丧失。这种疾病是由于在大脑中两种类型的异常不可溶聚集物的积累，从而破坏记忆和认知技能：细胞外的ß-淀粉样斑块和细胞内的神经纤维缠结。这些聚集物破坏大脑神经元之间的复杂相互作用，最终导致神经元的死亡和大脑容量的严重萎缩。[73]

致病的ß-淀粉样蛋白属于朊蛋白的类别，它吸引新的ß-淀粉样“种子”形成不可溶的低聚物，并在大脑中蔓延，从而启动破坏过程的连锁反应。然而，与“疯牛病”(牛海绵状脑病，或BSE)朊蛋白不同，与AD相关的淀粉样变性是不传染的，无法在个体之间传播。[74]神经纤维缠结是通过tau蛋白的超磷酸化形式的低聚化而在细胞内形成的，在正常情况下，它集中在轴突中，负责维持微管的结构。在这种疾病中，tau蛋白错误折叠，并错误定位在神经元胞体中。[75]



β-淀粉样蛋白是淀粉样斑块的主要成分。

阿茨海默病以两种形式存在：早发性AD(EOAD，30–60岁)和晚发性AD(LOAD)(表2)。EOAD主要是一种遗传病，而LOAD是一种偶发病，与不同突变之间的复杂相互作用存在关联。

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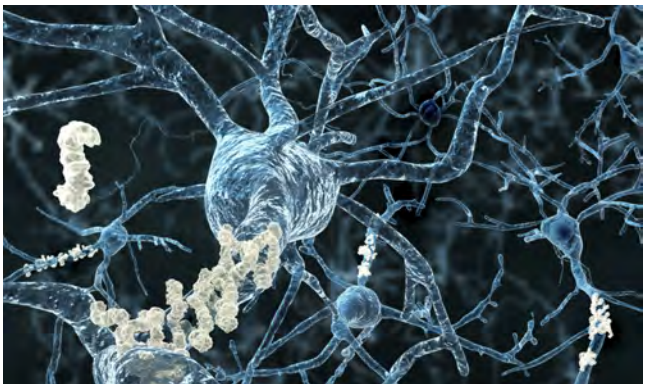
表2：AD的类型

疾病类型	发作年龄	病例百分比	疾病特征
早发性AD（EOAD）	30–60岁	2%–5%	主要是遗传[76]
晚发性AD（LOAD）	＞60岁	95%–98%[77]	表观遗传标记的强烈作用，如DNA甲基化[78]

EOAD与三个基因中的突变相关联：淀粉样前体蛋白（APP，整体I型跨膜糖蛋白）和早老蛋白PSEN1和PSEN2。然而，据报道这些突变只占了所有AD病例的不到2%。[79,80]这些基因中的突变下调了APP通路，导致ß-淀粉样蛋白的斑块累积。[81]有意思的是，APP的一些突变也许能防止AD，[82,83]强调了深度遗传分析和疾病关联研究的重要性。

直到最近，LOAD也只有一种已知的遗传风险因素：即载脂蛋白E基因（APOE）的E4变异。[84]带有两个拷贝的APOE4的个体（人群的2%）在85岁时发展成LOAD的风险高达60%，而带有一个拷贝的变异的个体（人群的25%）的风险为30%。[85]每个额外的APOE4拷贝将发展成AD的风险提高了三倍或以上。[86]传统GWAS可能错过了那些对LOAD病因有较大影响的低频率变异。基于序列的关联研究也许能鉴定复杂疾病的风险等位基因，且这些研究有望阐明效应量大的低频率变异。[87]



细胞外的淀粉样斑块相互黏连，并与神经元黏连。它们破坏神经元网络，导致神经元死亡和大脑活动的损伤。

一个有趣的实验方法提议在一组精心挑选的AD风险增高的个体上开展WES，然后是基因分型和重测序分析。[88]

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79. Lu H., Liu X., Deng Y. and Qing H. (2013) DNA methylation, a hand behind neurodegenerative diseases. Front Aging Neurosci 5:85
80. Guerreiro R. J., Gustafson D. R. and Hardy J. (2012) The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. Neurobiol Aging 33:437-456
81. Lu H., Liu X., Deng Y. and Qing H. (2013) DNA methylation, a hand behind neurodegenerative diseases. Front Aging Neurosci 5:85
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86. Medland S. E., Jahanshad N., Neale B. M. and Thompson P. M. (2014) Whole-genome analyses of whole-brain data: working within an expanded search space.
Nat Neurosci 17:791-800
87. Mitsui J. and Tsuji S. (2014) Genomic Aspects of Sporadic Neurodegenerative Diseases. Biochem Biophys Res Commun 452:221-225
88. Cruchaga C., Karch C. M., Jin S. C., Benitez B. A., Cai Y., et al. (2014) Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. Nature 505:550-554

衰老和AD与一连串的表观遗传改变相关联，如异常的DNA甲基化和组蛋白修饰。[89]这些改变可能在某些环境条件下发生，如中风、[90]高血压、II型糖尿病、肥胖、[91]重金属暴露、[92,93]头部损伤、免疫相关蛋白，[94,95,96]以及母体病毒感染[97-100]（详见表观遗传修饰）。

目前有关AD的两项最大型GWAS分析表明，在与AD、胆固醇代谢和免疫反应相关的通路中，致病基因之间存在明显的重叠。[101]神经退行往往伴随着小胶质细胞和单核细胞在淀粉样斑块和濒死神经元周围积累。[102]此外，神经元表达一些通常属于免疫系统的分子，暗示神经元和免疫系统之间存在复杂的相互作用。[103]（详见生物学：免疫力）

综述

Guo J. L. and Lee V. M. (2014) Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. Nat Med 20: 130-138

Medland S. E., Jahanshad N., Neale B. M. and Thompson P. M. (2014) Whole-genome analyses of whole-brain data: working within an expanded search space. Nat Neurosci 17: 791-800

Mitsui J. and Tsuji S. (2014) Genomic Aspects of Sporadic Neurodegenerative Diseases. Biochem Biophys Res Commun 452: 221-225

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Eisenberg D. and Jucker M. (2012) The amyloid state of proteins in human diseases. Cell 148: 1188-1203

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Huang Y. and Mucke L. (2012) Alzheimer mechanisms and therapeutic strategies. Cell 148: 1204-1222

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“双胞胎研究支持了表观遗传机制调控AD风险的想法。” Huang and Mucke 2012

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Cruchaga C., Karch C. M., Jin S. C., Benitez B. A., Cai Y., et al. (2014) Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. Nature 505: 550-554

LOAD的研究人员已经鉴定出一些遗传风险变异，但大多影响较小。为了鉴定影响大的低频率编码变异，这项研究使用Illumina的HiSeq系统，对14个LOAD大家族和病例-对照数据集进行WES。作者发现了PLD3的稀有变异，它与两个独立家庭的疾病状态隔离，并在七对独立的病例-对照组中将AD风险提高一倍。作者开展后续的功能检测以确定PLD3的影响，发现它影响APP加工。

Illumina的技术：GoldenGate，HiSeq 2000

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De Jager P. L., Srivastava G., Lunnon K., Burgess J., Schalkwyk L. C., et al. (2014) Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. Nat Neurosci 17: 1156-1163

DNA甲基化是一种遗传机制，它可能影响基因表达，因此与疾病易感性相关。这项研究利用Illumina的HumanMethylation450芯片和Illumina HiSeq 2000上的亚硫酸氢盐测序，研究了表观基因组对AD发生和发展的影响。作者发现DNA甲基化改变与AD症状发生前的积累之间存在一些重复且功能上经过验证的关联。他们猜测，观察到的DNA甲基化改变可能参与了AD的发生。

Illumina的技术：HumanMethylation450，HiSeq 2000

Lunnon K., Smith R., Hannon E., De Jager P. L., Srivastava G., et al. (2014) Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. Nat Neurosci 17: 1164-1170
在这项AD甲基化变异的研究中，作者利用Illumina的HumanMethylation450芯片来鉴定多个组织中全基因组范围的DNA甲基化状态。根据122个供体样本的结果，作者比较了四个大脑区域和全血的甲基化状态。他们在与AD神经病理相关的ANK1基因中发现了CpG位点存在皮质特异的超甲基化的证据。

Illumina的技术：HumanMethylation450，Human Gene Expression BeadArray

Raj T., Ryan K. J., Replogle J. M., Chibnik L. B., Rosenkrantz L., et al. (2014) CD33: increased inclusion of exon 2 implicates the Ig V-set domain in Alzheimer's disease susceptibility. Hum Mol Genet 23: 2729-2736
对疾病的预测治疗靶点的鉴定需要对鉴定出的遗传疾病变异进行后续的功能鉴定。在这项研究中，作者利用队列人群的表达数据对一个之前鉴定出的AD风险等位基因进行详细研究，这些人群已根据Illumina Infinium芯片鉴定出的遗传风险变异进行了分层。作者发现，风险等位基因rs3865444（C）导致单核细胞上CD33的表面密度更高。这个风险等位基因与CD33第2外显子的表达升高强烈相关，这有可能是风险变异的功能影响。

Illumina的技术：Human OmniExpress

Bai B., Hales C. M., Chen P. C., Gozal Y., Dammer E. B., et al. (2013) U1 small nuclear ribonucleoprotein complex and RNA splicing alterations in Alzheimer's disease. Proc Natl Acad Sci U S A 110: 16562-16567
许多神经退行性疾病的特点是不可溶的蛋白聚集物的沉积。AD中ß-淀粉样蛋白和tau蛋白的普遍存在已经促进了淀粉样级联和tau假说的发展，这些在AD病理研究和疗法开发中占主导地位。这项研究通过质谱分析和转录组测序，研究了AD大脑中不可溶的蛋白质组。作者发现有36种蛋白在疾病中累积，并发现与轻度认知障碍的蛋白聚集物存在相似性。

Illumina的技术：HiSeq 2000（mRNA测序）

Cruchaga C., Kauwe J. S., Harari O., Jin S. C., Cai Y., et al. (2013) GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. Neuron 78: 256-268
AD的病情进展可通过脑脊液中tau的磷酸化苏氨酸181（ptau）来监控。为了鉴定与ptau升高相关的遗传机制，作者开展了目前最大的GWAS研究，招募了1269名参与者。他们利用Illumina OmniExpress芯片对参与者进行基因分型，并测定tau/ptau的水平。作者鉴定出三个与CSF tau和ptau有着全基因组意义的位点；其中一个在独立数据集中表现出与AD风险强烈关联。

Illumina的技术：Human610-Quad，HumanOmniExpress

Lambert J. C., Ibrahim-Verbaas C. A., Harold D., Naj A. C., Sims R., et al. (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45: 1452-1458
AD是一种渐进性的神经疾病，主要影响老年人。之前的分析已经鉴定出与LOAD相关的11个基因组位点。为了搜索更多的风险位点，作者利用已发表的数据集开展了大型的GWAS元分析，这些数据是来自~17000名AD病例和~37000名对照的Illumina iSelect基因型数据。分析发现了19个明显相关的位点，其中11个之前并未与LOAD相关联。

Illumina的技术：iSelect

Zhang B., Gaiteri C., Bodea L. G., Wang Z., McElwee J., et al. (2013) Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell 153: 707-720

尽管深入研究了几十年，但LOAD背后的致病机制仍然不清楚。这项研究利用Illumina HiSeq对大脑标本和细胞系样本开展RNA-Seq，鉴定与LOAD相关的分子系统。作者通过LOAD病理学构建了等级次序的分子相互作用网络，并鉴定出免疫和小胶质细胞特异的模块，它们主要包括与病原体吞噬相关的基因。作者建议将致病网络结构作为应答基因扰动的有用预测器，以及检验LOAD背后的疾病机制模型的框架。

Illumina的技术：HiSeq 2000（mRNA测序），HT-12 Expression BeadChip，HumanHap 650Y

Sherva R., Tripodis Y., Bennett D. A., Chibnik L. B., Crane P. K., et al. (2014) Genome-wide association study of the rate of cognitive decline in Alzheimer's disease. Alzheimers Dement 10: 45-52

Guffanti G., Torri F., Rasmussen J., Clark A. P., Lakatos A., et al. (2013) Increased CNV-region deletions in mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects in the ADNI sample. Genomics 102: 112-122

Jonsson T., Atwal J. K., Steinberg S., Snaedal J., Jonsson P. V., et al. (2012) A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488: 96-99

帕金森病

帕金森病（PD）是仅次于AD的第二种常见的神经退行性疾病。[104]美国大约有100万人罹患此病，而全球患病人数超过400万。在工业化国家，60岁以上的人群中PD的发病率预计在1%–2%，而85岁以上的人群达到3%–5%。只有1%的PD病例是家族性的；其余都是散发的。[105]它的典型症状包括肌肉僵硬、运动迟缓（动作慢）、颤抖和姿势不稳。[106]随着疾病发展，可能出现记忆丧失，而症状逐渐变得与AD非常相似。[107]PD患者可能形成各种神经精神疾病，如焦虑、冷漠、抑郁、幻觉和妄想。[108]

PD的诊断主要依靠症状，目前还没有使用分子检测。[109]在PD出现明显症状之前，大多数神经元表现出退化的功能失调或丧失，[110]因此早期检测有望明显改善预后。最近，一些研究小组报道了侵入性极低的诊断系统的开发，可以通过外周血、浆细胞样骨髓来源细胞（PBMC）或CSF来检测AD[111,112,113]和PD[114]。诊断的目标分子包括真核起始因子2（EIF2）[115]、表皮生长因子（EGF）[116,117]和淀粉样ß1-42[118,119]。

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116. Chen-Plotkin A. S., Hu W. T., Siderowf A., Weintraub D., Goldmann Gross R., et al. (2011) Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease. Ann Neurol 69:655-663
117. Irwin D. J., Lee V. M. and Trojanowski J. Q. (2013) Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. Nat Rev Neurosci 14:626-636
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PD的生物学原因包括黑质多巴胺能神经元和纹状体投射神经元的逐渐丧失。[120]PD的主要病理学指标是路易体的积累，它主要通过在多个脑区中表达的小蛋白-突触核蛋白的自我组装而形成。[121]路易体的斑块与AD相似，随着疾病的发展，它们蔓延到其他脑区（如边缘和新皮层区），并导致神经元死亡。[122]

年龄是PD发展的一个主要风险因素。[123]超过80%的PD患者最终将发展成痴呆，这种疾病被称为帕金森病痴呆（PDD）。人们认为，这种痴呆的主要原因是来自脑干的纤维状α-突触核蛋白扩散到边缘和新皮层结构。[124]此外，超过50%的PDD患者形成淀粉样ß斑块和神经纤维缠结，这是AD的典型特征。[125]PDD和AD的双重病理增加了疾病的恶性程度，使得预后明显恶化。

表3列出了六个基因中的突变，它们与PD存在关联。[126,127]

表3：与PD关联的基因突变

基因名称	蛋白名称	功能作用
SNCA	α-突触核蛋白	对正常的大脑活动至关重要：参与学习、发育、细胞分化、神经可塑性以及多巴胺吸收的调控[128,129,130]。家族性和散发性PD都有风险因素[131,132]。
PARK2	PARK2（Parkin）	一个复合物中的核心元件，将细胞内蛋白泛素化，以便降解[133]。
PINK1	PTEN诱导的激酶蛋白1	以线粒体为目标的激酶。保护细胞免受应激诱导的线粒体功能障碍、氧化应激和凋亡[134]。
UCHL1	泛素羧基末端水解酶L1	神经元特异的泛素羧基末端水解酶。让泛素链变回泛素单体，在单泛素化的α-突触核蛋白上添加泛素[135]。
DJ1（PARK7）	PARK7	调控α-突触核蛋白的聚集[136]。
LRRK2	富亮氨酸的重复丝氨酸/苏氨酸蛋白激酶2	LRRK2可能解除对α-突触核蛋白磷酸化的调控，导致PD发病的开始[137]。

120. Lu H., Liu X., Deng Y. and Qing H. (2013) DNA methylation, a hand behind neurodegenerative diseases. Front Aging Neurosci 5:85
121. Huang Y. and Mucke L. (2012) Alzheimer mechanisms and therapeutic strategies. Cell 148:1204-1222
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125. Irwin D. J., Lee V. M. and Trojanowski J. Q. (2013) Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. Nat Rev Neurosci 14:626-636
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家族性的PD可能通过常染色体显性或常染色体隐性的方式遗传。前者与α-突触核蛋白和LRRK2相关联，而后者与Parkin、PINK1、DJ1和ATP13A2相关联。深入了解这些基因在PD中的作用，将有助于基因组分析的开发，作为家族性PD的早期诊断工具。[138]

目前，控制PD患者临床症状的主要方法是用L-DOPA、卡比多巴和单胺氧化酶B抑制剂来替换多巴胺。[139]不过，这种治疗的效果是短暂的，患者会形成耐药性，造成后续没有疗法可选。PD的基因组分析有望改善PD的治疗。NGS实现了一种新的治疗方法，它根据mirtrons：miRNA依赖剪接来生成前体，而不是Dicer和RNA诱导沉默复合物（RISC），从而通过一种RNA干扰的途径来靶定疾病特异的mRNA。[140]通过这种方法，研究人员对85%以上的α-突触核蛋白和LRRK2实现了沉默。

在散发性PD患者的黑质、皮层和壳核中，α-突触核蛋白的甲基化减少。[141]六个风险位点与近端基因表达或DNA甲基化相关联。[142]（详见表观遗传修饰）

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路易体痴呆（DLB）、PD和AD在临床和神经病理上存在相似性，说明这些疾病可能有相同的病因。为了检验这个假说，这项研究利用Illumina的NeuroX定制芯片来检验54个基因组区域的关联，这些区域曾与大规模的DLB病例和对照队列中与PD或AD相关联。作者发现APOE是DLB的主要遗传风险因素，还有其他一些潜在的风险位点。总的来说，这些结果表明影响DLB病因的一些遗传因素与AD和PD相同，但这些位点可能以不同的方式起作用。

Illumina的技术：Infinium HumanExome BeadChip

Hollerhage M., Goebel J. N., de Andrade A., Hildebrandt T., Dolga A., et al. (2014) Trifluoperazine rescues human dopaminergic cells from wild-type alpha-synuclein-induced toxicity. Neurobiol Aging 35: 1700-1711

PD是最常见的神经退行性运动障碍。为了研究PD发展中α-突触核蛋白介导的毒性，作者开发出一种新的细胞系模型，其中野生型α-突触核蛋白的中度过表达导致人有丝分裂后的DA神经元逐渐死亡。利用Illumina BeadArray来监控基因表达，作者发现，激活人DA中脑神经元的自噬可避免α-突触核蛋白诱导的细胞死亡。安定剂三氟拉嗪作为大自噬的激活剂，也许是潜在的治疗靶点。

Illumina的技术：Human Gene Expression BeadArray

Mencacci N. E., Isaias I. U., Reich M. M., Ganos C., Plagnol V., et al. (2014) Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain 137: 2480-2492

GTP环化水解酶1（由GCH1基因编码）也许与PD的风险增高存在关联。作者采集了1,318名PD病例和5,935名对照个体的WES数据，评估了GCH1变异的频率。通过分析，他们从GCH1中鉴定出11个不同的杂合变异，其中包括四个之前已报道的致病变异和七个临床相关性未知的变异。与对照相比，GCH1变异的频率明显增高，表明GTP环化水解酶1缺乏的临床相关性。

Illumina的技术：HiSeq 2000

Nalls M. A., Pankratz N., Lill C. M., Do C. B., Hernandez D. G., et al. (2014) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 46: 989-993

到目前为止只发现了关于PD一小部分的遗传可能性。这项研究开展了GWAS的元分析，以搜索与疾病相关的新位点。利用Illumina的基因分型芯片，作者鉴定出24个位点，它们既具有统计学意义，又能在实验中重复。其中六个位点之前并无报道称与PD相关，作者预计这些位点的累积风险很可观（优势比 = 3.31）。

Illumina的技术：ExomeChip，HumanOmniExpress，HumanHap550，Human610-Quad，HumanHap660W-Quad，HumanMethylation27，Human Gene Expression BeadArray

Chung S. J., Armasu S. M., Anderson K. J., Biernacka J. M., Lesnick T. G., et al. (2013) Genetic susceptibility loci, environmental exposures, and Parkinson's disease: a case-control study of gene-environment interactions. Parkinsonism Relat Disord 19: 595-599

人们认为，PD易感性与遗传和环境因素的组合相关。这项研究调查了已知的遗传风险因素与环境暴露（杀虫剂施用、吸烟、饮酒和喝咖啡）之间的潜在相互作用。利用Illumina的GoldenGate基因分型芯片，作者对1098个PD病例和1098个对照进行基因分型，并开展相互作用分析。他们发现，所研究的基因型与环境风险因素之间的配对相互作用的证据有限；不过，未来需要更大的样本量来确认对PD易感性的影响。

Illumina的技术：BeadArray Reader，DNA Test Panel

Karlsson M. K., Sharma P., Aasly J., Toft M., Skogar O., et al. (2013) Found in transcription: accurate Parkinson's disease classification in peripheral blood. J Parkinsons Dis 3: 19-29

PD的发病率随着年龄的增加而升高。为了开发早期检测PD的血液型检测，作者利用Illumina的Gene Expression BeadArray对PD患者和对照的队列开展了大规模的基因表达研究，以开发预测模型并检验其准确性。通过交叉验证研究，他们发现PD患者能与健康对照正确区分，与临床诊断相比，准确率达88%。这些结果表明了开发PD的血液型基因表达检测的潜力。

Illumina的技术：Human Gene Expression BeadArray

Ryan S. D., Dolatabadi N., Chan S. F., Zhang X., Akhtar M. W., et al. (2013) Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1alpha transcription. Cell 155: 1351-1364

之前有报道称PD和线粒体毒素暴露之间存在着关联。在这项研究中，作者利用干细胞模型来鉴定毒素的反应，采用Illumina的BeadArray开展基因表达分析。作者发现了一个通路，其中基础和毒素诱导的氮化/氧化应激导致转录因子MEF2C的S-亚硝基化。他们发现这些改变促使线粒体功能失调和凋亡性细胞死亡，表明这是PD的机制和潜在治疗靶点。

Illumina的技术：Human Gene Expression BeadArray

Ganat Y. M., Calder E. L., Kriks S., Nelander J., Tu E. Y., et al. (2012) Identification of embryonic stem cell-derived midbrain dopaminergic neurons for engraftment. J Clin Invest 122: 2928-2939

Rousseaux M. W., Marcogliese P. C., Qu D., Hewitt S. J., Seang S., et al. (2012) Progressive dopaminergic cell loss with unilateral-to-bilateral progression in a genetic model of Parkinson disease. Proc Natl Acad Sci U S A 109: 15918-15923

Sibley C. R., Seow Y., Curtis H., Weinberg M. S. and Wood M. J. (2012) Silencing of Parkinson's disease-associated genes with artificial mirtron mimics of miR-1224.Nucleic Acids Res 40: 9863-9875

遗传机制

精神分裂症、自闭症、PD和AD都是复杂的疾病，由多个遗传和环境因素的复杂相互作用所驱动。复杂疾病的病因是所有这些因素的总和，包括体细胞（非遗传）突变、遗传突变、表观遗传修饰、小RNA、免疫力及其他因素。NGS作为一种工具，可测定大部分的贡献因素。未来的挑战是将这些结果汇聚成对这些复杂疾病的一致观点。[143]

拷贝数变异

CNV是精神疾病中最常见的突变之一。采用芯片方法已获得了一些显著成效，特别是定位CNV。[144]然而，芯片不能检测平衡易位，而荧光原位杂交（FISH）技术的分辨率又有限。在健康和患病个体的基因组中，平衡易位的真实程度只能通过NGS来发现。双端测序和mate-pair测序在定位基因组重排上特别有效。[145]两个研究团队估计，与AD相关的CNV数量在130至300个目标位点之间。[146,147]CNV还在精神分裂症和双相障碍中发挥关键的作用。[148-151]最近对大脑组织中的单细胞和神经元的研究发现，正常大脑组织中的大部分（≥95%）神经元是整倍体的。不过，一名半侧巨脑症（HMG）患者因染色体1q上带有体细胞CNV，意外发现20%的神经元存在1q四体异常。这种现象表明大脑中的不同细胞可能带有不同的突变，而少数细胞中的CNV足以导致广泛的大脑功能异常。[152]这么高的复杂性唯有通过单细胞测序方法来解决（详见生物学：单细胞）。

大多数的新发结构变异都归因于新的转座子插入。外显子组测序研究表明，导致ASD的单核苷酸变异（SNV）的水平升高与父亲年龄呈阳性相关。[153]CNV也可能与不同位点的其他CNV或其他点突变一起导致疾病，但鉴定这些相互作用却颇具挑战性。[154]为了解释多方面的影响，一些研究小组提出了“二次打击”假说，与癌症类似。[155,156]

> “最近的技术进步使人们能够以超级快速且廉价的方式对分散在基因组内的大量标记进行拷问。” Bras et al.2012

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148. Malhotra D., McCarthy S., Michaelson J. J., Vacic V., Burdick K. E., et al. (2011) High frequencies of de novo CNVs in bipolar disorder and schizophrenia. Neuron 72:951-963
149. Priebe L., Degenhardt F. A., Herms S., Haenisch B., Mattheisen M., et al. (2012) Genome-wide survey implicates the influence of copy number variants (CNVs) in the development of early-onset bipolar disorder. Mol Psychiatry 17:421-432
150. Zhang D., Cheng L., Qian Y., Alliey-Rodriguez N., Kelsoe J. R., et al. (2009) Singleton deletions throughout the genome increase risk of bipolar disorder. Mol Psychiatry 14:376-380
151. Stefansson H., Meyer-Lindenberg A., Steinberg S., Magnusdottir B., Morgen K., et al. (2014) CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505:361-366
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155. Nava C., Keren B., Mignot C., Rastetter A., Chantot-Bastaraud S., et al. (2014) Prospective diagnostic analysis of copy number variants using SNP microarrays in individuals with autism spectrum disorders. Eur J Hum Genet 22:71-78
156. Gau S. S., Liao H. M., Hong C. C., Chien W. H. and Chen C. H. (2012) Identification of two inherited copy number variants in a male with autism supports two-hit and compound heterozygosity models of autism. Am J Med Genet B Neuropsychiatr Genet 159B:710-717

斯堪的纳维亚家族被广泛用作自闭症和精神分裂症GWAS的对象。这种选择是因为斯堪的纳维亚人的种族一致性，并且这些国家建立了完善的新生儿血液样本登记系统（如丹麦新生儿筛查生物样本库）和健康档案。[157]

综述

Cai X., Evrony G. D., Lehmann H. S., Elhosary P. C., Mehta B. K., et al. (2014) Single-Cell, Genome-wide Sequencing Identifies Clonal Somatic Copy-Number Variation in the Human Brain. Cell Rep 8: 1280-1289

Gilissen C., Hehir-Kwa J. Y., Thung D. T., van de Vorst M., van Bon B. W., et al. (2014) Genome sequencing identifies major causes of severe intellectual disability. Nature 511: 344-347

Jacquemont S., Coe B. P., Hersch M., Duyzend M. H., Krumm N., et al. (2014) A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet 94: 415-425

Rosti R. O., Sadek A. A., Vaux K. K. and Gleeson J. G. (2014) The genetic landscape of autism spectrum disorders. Dev Med Child Neurol 56: 12-18

Malhotra D. and Sebat J. (2012) CNVs: harbingers of a rare variant revolution in psychiatric genetics. Cell 148: 1223-1241

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Fromer M., Pocklington A. J., Kavanagh D. H., Williams H. J., Dwyer S., et al. (2014) De novo mutations in schizophrenia implicate synaptic networks. Nature 506: 179-184

在精神分裂症的已知风险等位基因中，唯一明确增加风险的因素是染色体CNV，它们涉及到数千个DNA碱基的缺失或重复。此研究调查了小的新发突变的影响，它们影响一个或几个核苷酸。利用Illumina HiSeq对623个精神分裂症家系进行WES测序，作者评估了新发突变率以及精神分裂症、智力障碍和ASD的共同遗传病因。他们获得了一些线索，表明病因机制有共同之处。

Illumina的技术：HiSeq（外显子组测序）

157. Szatkiewicz J. P., O'Dushlaine C., Chen G., Chambert K., Moran J. L., et al. (2014) Copy number variation in schizophrenia in Sweden. Mol Psychiatry 19:762-773

Gaugler T., Klei L., Sanders S. J., Bodea C. A., Goldberg A. P., et al. (2014) Most genetic risk for autism resides with common variation. Nat Genet 46: 881-885
尽管ASD已经被广泛研究，但遗传可能性的比例和性质仍然不清楚。这项研究分析了迄今为止最大的自闭症队列数据，包括160万个瑞典家庭（至少有两个孩子）和大约5700名经过严格的自闭症诊断的个体。利用Illumina的SNP芯片，作者研究了罕见和常见遗传变异对疾病的贡献。他们的结论是，遗传可能性约为52.4%，而常见变异是最大的贡献因素。罕见的新发突变对个体患病的贡献可观，但它们对倾向差异的贡献是中度的，约为2.6%。

Illumina的技术：OmniExpress

Karayannis T., Au E., Patel J. C., Kruglikov I., Markx S., et al. (2014) Cntnap4 differentially contributes to GABAergic and dopaminergic synaptic transmission. Nature 511: 236-240
为了了解神经系统疾病的发展，人们以神经细胞中表达的蛋白质为背景，研究了遗传影响。在这项研究中，作者鉴定了CNTNAP4敲除对小鼠行为和发育的影响，并将这些结果与人类CNTNAP2基因所在区域的CNV相关联。作者发现，CNTNAP4位于突触前，而它的损失导致皮层小清蛋白（PV）阳性的氨基丁酸能篮状细胞的产量减少。此外，CNTNAP4突变小鼠表现出这些神经群体的缺陷，以及感知运动门控和修饰的内表型。

Illumina的技术：HumanHap550，HumanOmni1-Quad

Stefansson H., Meyer-Lindenberg A., Steinberg S., Magnusdottir B., Morgen K., et al. (2014) CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505: 361-366
某些CNV促成了精神分裂症和自闭症的发病。在这项研究中，作者调查了这些CNV对与上述疾病分离的表型的影响。在一项涉及到近三分之一冰岛人群的大型群体研究中（n = 101655），作者利用Illumina的SNP芯片来检验CNV与认知障碍、诵读困难、计算困难和大脑结构改变的关联。他们发现，15q11.2（BP1-BP2）的缺失影响了大脑结构，其模式与精神分裂症和诵读困难的首发精神病一致。

Illumina的技术：HumanHap300，HumanCNV370-Duo，HumanHap650Y，Human1M，HumanOmni2.5，HumanOmniExpress，HumanOmni1S

Chapman J., Rees E., Harold D., Ivanov D., Gerrish A., et al. (2013) A genome-wide study shows a limited contribution of rare copy number variants to Alzheimer's disease risk. Hum Mol Genet 22: 816-824
AD是最常见的痴呆症形式，尽管遗传上很复杂，但它也是遗传性很高的。这项研究利用Illumina Infinium芯片探索了CNV的流行状况，以确定罕见CNV是否在AD易感性中扮演角色。尽管作者发现了之前的AD研究所强调的位点，但他们并没有发现CNV对AD病情发展的明显贡献。

Illumina的技术：Human610-Quad

Lionel A. C., Tammimies K., Vaags A. K., Rosenfeld J. A., Ahn J. W., et al. (2014) Disruption of the ASTN2/TRIM32 locus at 9q33.1 is a risk factor in males for autism spectrum disorders, ADHD and other neurodevelopmental phenotypes. Hum Mol Genet 23: 2752-2768

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选择性剪接

据估计，高达94%的多外显子基因经过了选择性剪接，而不正确的剪接至少导致15%的病例。[158,159]选择性剪接是指mRNA前体的外显子被分组（剪接）成不同的排列方式，所产生的成熟mRNA可编码结构上和功能上不同的蛋白变体。高通量基因组分析工具（如外显子芯片和RNA-Seq）的出现实现了选择性剪接事件的鉴定，而之前利用传统芯片无法检测。

外显子芯片可区分不同的异构体。[160]不过，这项技术也有一些内在的限制，比如只能检测之前测序过的基因组的已知剪接变体、信噪比低、动态范围有限，以及交叉杂交。当这种技术与mRNA测序结合使用，它的全部力量才能释放出来，以单碱基分辨率对外显子和转录本边界进行鉴定，并检测新颖的转录本。在这种方法中，mRNA首先被转化成cDNA，之后与独特的接头连接，并以大规模并行的方式测序。[161]

通常与AD相关联的大多数基因都有多个剪接变体，而其中一些变体是致病的。[162,163,164]对于PD，选择性剪接在PARK2、SNCA和SRRM2基因中检测到。尽管PARK2的全部三个剪接变体都被认为是非致病的，但人们猜想这三个转录本的比例变化可能决定了疾病易感性。[165]最后，还有一些证据表明，与AD易感基因相对应的未剪接mRNA在AD患者的大脑中积累，这是由于U1小核糖核蛋白（U1 snRNP）发生突变，它是剪接复合物中的一个组分。多个U1 snRNP亚基形成了AD的细胞质缠结聚集。[166]

人类大脑的RNA样本通常是从尸体中获得的，这就为遗传分析带来了RNA质量不佳的问题。不过，人们也许可以对大脑及外周器官和组织（如血液）中的RNA和蛋白表达进行关联研究，以实现神经退行性疾病的早期、无创诊断，这与先前建立的前列腺癌诊断方法相似。[167-170]

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表观遗传修饰

由于检测全基因组表观遗传模式的芯片和NGS方案的开发，表观遗传改变在精神疾病发生和发展中的广泛作用近来渐趋明显。这种作用在神经退行性疾病中似乎特别强烈；然而，近期在精神疾病中发现的一些表观遗传模式可能对更好地了解这些疾病的原因和模式很关键。研究神经系统疾病的表观遗传学的困难之处在于这些特征只能在死后检测，而样本稳定性和这些修饰往往受损。[171]

基因组印记是表观遗传修饰终身存在的一个例子。[172]第一个与ASD相关联的基因——SHANK3有五个CpG岛，表现出大脑和细胞类型特异的DNA甲基化模式。[173,174,175]在这个基因中也观察到类似的组蛋白乙酰化的特异性。[176]这些修饰以异构体特异的模式调控SHANK3基因的表达。[177]一些研究小组在自闭症患者的尸体样本中独立鉴定出其他多个甲基化差异的区域（DMR），这些区域代表多样化的基因区域，如DNase超敏位点和选择性转录终止位点。[178,179,180]这些研究为揭开ASD等复杂疾病的机制提供了更多的证据。

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衰老和AD（特别是LOAD）也与各种表观遗传改变相关联，包括异常的DNA甲基化和组蛋白修饰。[181,182]这些改变可能由生理和环境条件引发，如中风[183]、高血压、II型糖尿病、肥胖[184]、重金属暴露[185,186]，以及头部损伤[187]。例如，氧化应激可能导致AD大脑中DNA甲基化和脱甲基化之间的不平衡。[188]在AD患者死后的大脑中，也观察到组蛋白尾修饰的变化（主要是颞叶中H3乙酰化的水平降低，而组蛋白脱乙酰基酶类HDAC2和HDAC6的水平升高）。[189,190,191]利用治疗剂来靶定这些组蛋白修饰，是一种大有潜力的AD治疗策略。[192]小鼠实验表明，在学习任务后用药物抑制小鼠海马区的DNA甲基化，破坏了记忆巩固[193]，而组蛋白乙酰化的提高有相反的作用：它通过增加年迈小鼠中与学习相关基因的表达，增强了学习和记忆。[194,195]

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表观遗传修饰也在PD的发病中起关键的作用。之前曾在散发性PD患者的黑质、皮层和壳核中检测到编码α-突触核蛋白的SNCA基因的甲基化水平降低。[196,197] α-突触核蛋白直接与组蛋白H3结合，抑制组蛋白乙酰化。[198]

综述

Coppede F. (2014) The potential of epigenetic therapies in neurodegenerative diseases. Front Genet 5: 220

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DNA甲基化是一种遗传机制，它可能影响基因表达，因此与疾病易感性相关。这项研究利用Illumina的HumanMethylation450芯片和Illumina HiSeq 2000上的亚硫酸氢盐测序，研究了表观基因组对AD发生和发展的影响。作者发现DNA甲基化改变与AD症状发生前的积累之间存在一些重复且功能上经过验证的关联。他们猜测，观察到的DNA甲基化改变可能参与了AD的发生。

Illumina的技术：HumanMethylation450，HiSeq 2000

Hollerhage M., Goebel J. N., de Andrade A., Hildebrandt T., Dolga A., et al. (2014) Trifluoperazine rescues human dopaminergic cells from wild-type alpha-synuclein-induced toxicity. Neurobiol Aging 35: 1700-1711

PD是最常见的神经退行性运动障碍。为了研究PD发展中α-突触核蛋白介导的毒性，作者开发出一种新的细胞系模型，其中野生型α-突触核蛋白的中度过表达导致人有丝分裂后的多巴胺能神经元逐渐死亡。利用Illumina BeadArray来监控基因表达，作者发现，激活人多巴胺能中脑神经元的自噬可避免α-突触核蛋白诱导的细胞死亡。安定剂三氟拉嗪作为大自噬的激活剂，也许是潜在的治疗靶点。

Illumina的技术：Human Gene Expression BeadArray

Ladd-Acosta C., Hansen K. D., Briem E., Fallin M. D., Kaufmann W. E., et al. (2014) Common DNA methylation alterations in multiple brain regions in autism. Mol Psychiatry 19: 862-871

遗传以及环境因素都是ASD的原因。在这项研究中，作者测定了19个自闭症病例的大脑组织中超过48.5万个CpG位点，鉴定出四个在全基因组范围明显不同的DMR。这项研究突出了一组新的受影响基因。

Illumina的技术：HumanMethylation450

Lunnon K., Smith R., Hannon E., De Jager P. L., Srivastava G., et al. (2014) Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. Nat Neurosci 17: 1164-1170

在这项AD甲基化变异的研究中，作者利用Illumina的HumanMethylation450k芯片来鉴定多个组织中全基因组范围的DNA甲基化状态。根据122个供体样本的结果，作者比较了四个大脑区域和全血的甲基化状态。他们在与AD神经病理相关的ANK1基因中发现了CpG位点存在皮质特异的超甲基化的证据。

Illumina的技术：HumanMethylation450k，Human Gene Expression BeadArray

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Nalls M. A., Pankratz N., Lill C. M., Do C. B., Hernandez D. G., et al. (2014) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 46: 989-993

到目前为止只发现了关于PD一小部分的遗传可能性。这项研究开展了GWAS的元分析，以搜索与疾病相关的新位点。利用Illumina的基因分型芯片，作者鉴定出24个位点，它们既具有统计学意义，又能在实验中重复。其中六个位点之前并无报道称与PD相关，作者预计这些位点的累积风险很可观（优势比 = 3.31）。

Illumina的技术：ExomeChip，HumanOmniExpress，HumanHap550，Human610-Quad，HumanHap660W-Quad，HumanMethylation27，Human Gene Expression BeadArray

Wong C. C., Meaburn E. L., Ronald A., Price T. S., Jeffries A. R., et al. (2014) Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. Mol Psychiatry 19: 495-503

小RNA

大脑中富含microRNA（miRNA），而神经元特异的miRNA控制了神经元分化、兴奋性和功能。[199]其他RNA，如非编码RNA（ncRNA），似乎在神经发育中起作用。

许多miRNA与AD和PD相关联，不仅在大脑中检测到，也在患病个体的外周组织中检测到。[200,201]这种现象表明，可开发侵入性极低的诊断工具，用于神经退行性疾病的早期预防。miRNA还被认为是针对AD病原体（如APP）的治疗剂。[202]miRNA分子可与适体、单克隆抗体、肽段或外泌体相结合或相关联，导入体内的特定细胞类型和组织。[203]

综述

Sekiyama K., Takamatsu Y., Waragai M. and Hashimoto M. (2014) Role of genomics in translational research for Parkinson's disease. Biochem Biophys Res Commun 452: 226-235

Maciotta S., Meregalli M. and Torrente Y. (2013) The involvement of microRNAs in neurodegenerative diseases. Front Cell Neurosci 7: 265

Mills J. D. and Janitz M. (2012) Alternative splicing of mRNA in the molecular pathology of neurodegenerative diseases. Neurobiol Aging 33: 1012 e1011-1024

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Raj T., Ryan K. J., Replogle J. M., Chibnik L. B., Rosenkrantz L., et al. (2014) CD33: increased inclusion of exon 2 implicates the Ig V-set domain in Alzheimer's disease susceptibility. Hum Mol Genet 23: 2729-2736

对预测治疗靶点的鉴定需要对已知的遗传疾病变异进行后续的功能鉴定。在这项研究中，作者利用队列人群的表达数据对一个之前鉴定出的AD风险等位基因进行详细研究，这些人群已根据Illumina Infinium芯片鉴定出的遗传风险变异进行了分层。作者发现，风险等位基因rs3865444（C）导致单核细胞上CD33的表面密度更高。这个风险等位基因与CD33第2外显子的表达升高强烈相关，这有可能是风险变异的功能影响。

Illumina的技术：OmniExpress

Bai B., Hales C. M., Chen P. C., Gozal Y., Dammer E. B., et al. (2013) U1 small nuclear ribonucleoprotein complex and RNA splicing alterations in Alzheimer's disease. Proc Natl Acad Sci U S A 110: 16562-16567

Many neurodegenerative diseases are characterized by deposition of insoluble protein aggregates.AD中ß-淀粉样蛋白和tau蛋白的普遍存在已经促进了淀粉样级联和tau假说的发展，这些在AD病理研究和疗法开发中占主导地位。这项研究通过质谱分析和转录组测序，研究了AD大脑中不可溶的蛋白质组。作者发现有36种蛋白在疾病中累积，并发现与轻度认知障碍的蛋白聚集物存在相似性。

Illumina的技术：HiSeq 2000（mRNA测序）

Li M. M., Jiang T., Sun Z., Zhang Q., Tan C. C., et al. (2014) Genome-wide microRNA expression profiles in hippocampus of rats with chronic temporal lobe epilepsy. Sci Rep 4: 4734

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基因变异

全基因组关联研究

全基因组关联研究（GWAS）通过比较大型病例和对照群体基因组中的等位基因频率，来鉴定常见病的易感等位基因。[204,205]这种方法获得了空前的临床相关数据，包括与AD和PD相关的大多数突变和变异。[207-211]然而，尽管目前已经有9,000多项GWAS研究发表，但这种方法只揭示了一小部分真正的遗传可能性。此外，GWAS可能错过表观遗传模式，如甲基化，它又将致病[213]SNV附近的基因误认为是致病的。以经济的价格对大型队列的整个基因组进行测序，有望产生更多的基因、通路和生物学见解，并有潜力鉴定致病突变。[214]NGS，无论是单独使用，还是与芯片结合使用，都能突破大部分限制，明显改善这些研究的结果。[215]

综述

Sharma M., Kruger R. and Gasser T. (2014) From genome-wide association studies to next-generation sequencing: lessons from the past and planning for the future. JAMA Neurol 71: 5-6

Keogh M. J. and Chinnery P. F. (2013) Next generation sequencing for neurological diseases: new hope or new hype? Clin Neurol Neurosurg 115: 948-953e>

Koboldt D. C., Steinberg K. M., Larson D. E., Wilson R. K. and Mardis E. R. (2013) The next-generation sequencing revolution and its impact on genomics. Cell 155: 27-38

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Karayannis T., Au E., Patel J. C., Kruglikov I., Markx S., et al. (2014) Cntnap4 differentially contributes to GABAergic and dopaminergic synaptic transmission. Nature 511: 236-240
为了了解神经系统疾病的发展，人们以神经细胞中表达的蛋白质为背景，研究了遗传影响。在这项研究中，作者鉴定了CNTNAP4敲除对小鼠行为和发育的影响，并将这些结果与人类CNTNAP2基因所在区域的CNV相关联。作者发现，CNTNAP4位于突触前，而它的损失导致皮层小清蛋白（PV）阳性的氨基丁酸能篮状细胞的产量减少。此外，CNTNAP4突变小鼠表现出这些神经群体的缺陷，以及感知运动门控和修饰的内表型。

Illumina的技术：HumanHap550，HumanOmni1

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到目前为止只发现了关于PD一小部分的遗传可能性。这项研究开展了GWAS的元分析，以搜索与疾病相关的新位点。利用Illumina的基因分型芯片，作者鉴定出24个位点，它们既具有统计学意义，又能在实验中重复。其中六个位点之前并无报道称与PD相关，作者预计这些位点的累积风险很可观（优势比 = 3.31）。

Illumina的技术：ExomeChip，HumanOmniExpress，HumanHap550，Human610-Quad，HumanHap660W-Quad，HumanMethylation27，Human Gene Expression BeadArray

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Cruchaga C., Kauwe J. S., Harari O., Jin S. C., Cai Y., et al. (2013) GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. Neuron 78: 256-268

AD的病情进展可通过脑脊液中tau的磷酸化苏氨酸181（ptau）来监控。为了鉴定与ptau升高相关的遗传机制，作者开展了目前最大的GWAS研究，招募了1269名参与者。他们利用Illumina OmniExpress芯片对参与者进行基因分型，并测定tau/ptau的水平。作者鉴定出三个与CSF tau和ptau有着全基因组意义的位点；其中一个在独立数据集中表现出与AD风险强烈关联。

Illumina的技术：Human610-Quad，HumanOmniExpress

新一代测序

在分析真核生物的DNA基因组时，新一代测序包括两种形式：WGS和WES。[216]WES与定制设计芯片的组合是大样本量的首选方法。[217]这种组合方法可有效地解决常见的遗传分析问题，如假基因、重复外显子，以及无法检测稀有和/或新颖突变。[218]此外，WES本身不足以弄清CNV，因为样本制备依赖非定量的PCR扩增。[219]然而，将WES和基因分型相结合的方法可解决这个难题。[220]

人们认为，采用多管齐下的方法，用WGS、蛋白质组学、表观基因组学来补充WES，可全面了解新发现的遗传变异的影响。稀有突变对疾病病理学的影响往往比常见突变更加强烈，而复杂疾病领域的这种影响特别值得关注。在发现新发突变时，NGS的力量进一步得以证明，这些突变在个体的一生中出现，更有可能对罕见病产生功能影响。尽管这些突变的出现似乎是随机的，但突变率及其对父母亲年龄[222]和其他环境因素的依赖只是这种技术带来的部分重要成果[223]。

通过分析循环肿瘤DNA，测序正成为疾病诊断所不可缺少的。不仅仅是DNA的序列，细胞数量的波动也往往与疾病病理和状态存在关联。“液体活检方法”能够检测血浆或巴氏（Pap）涂片中特定肿瘤类型的体细胞突变。[224,225]目前，通过外周血来检测PD[226]和AD[227,228]的方法正在开发中。在怀孕期间，胎儿完整基因组存在于母体血浆中[230]，这个新发现开启了无创产前诊断的新时代。

> “与研究常见突变的GWAS不同，测序促进了稀有突变的探索，而这些稀有突变往往与复杂表型相关联。”
>
> Koboldt et al.2013

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DNA甲基化是一种遗传机制，它可能影响基因表达，因此与疾病易感性相关。这项研究利用Illumina的HumanMethylation450k芯片和Illumina HiSeq 2000上的亚硫酸氢盐测序，研究了表观基因组对AD发生和发展的影响。作者发现DNA甲基化改变与AD症状发生前的积累之间存在一些重复且功能上经过验证的关联。他们猜测，观察到的DNA甲基化改变可能参与了AD的发生。

Illumina的技术：HumanMethylation450，HiSeq 2000

Fromer M., Pocklington A. J., Kavanagh D. H., Williams H. J., Dwyer S., et al. (2014) De novo mutations in schizophrenia implicate synaptic networks. Nature 506: 179-184

在精神分裂症的已知风险等位基因中，唯一明确增加风险的因素是染色体CNV，它们涉及到数千个DNA碱基的缺失或重复。此研究调查了小的新发突变的影响，它们影响一个或几个核苷酸。利用Illumina HiSeq对623个精神分裂症家系进行WES测序，作者评估了新发突变率以及精神分裂症、智力障碍和ASD的共同遗传病因。他们获得了一些线索，表明病因机制有共同之处。

Illumina的技术：HiSeq（外显子组测序）

Lee H., Lin M. C., Kornblum H. I., Papazian D. M. and Nelson S. F. (2014) Exome sequencing identifies de novo gain of function missense mutation in KCND2 in identical twins with autism and seizures that slows potassium channel inactivation. Hum Mol Genet 23: 3481-3489

许多研究报告了自闭症和癫痫的共患病，但这两种疾病之间的关系还不清楚。在这项研究中，作者利用外显子组测序对同卵双胞胎进行研究，他们都患有自闭症和严重的顽固性癫痫。作者在双胞胎中观察到KCND2基因的一个新型变异。这个新发突变位于编码Kv4.2钾离子通道的蛋白质上，作者在爪蟾卵母细胞中表达了这个突变蛋白，以观察功能影响。表达分析表明，突变明显破坏了钾离子通道的关闭状态失活，有力支持了KCND2作为此家族癫痫的致病基因。

Illumina的技术：HiSeq 2000，Illumina的双端测序文库制备方案

King I. F., Yandava C. N., Mabb A. M., Hsiao J. S., Huang H. S., et al. (2013) Topoisomerases facilitate transcription of long genes linked to autism. Nature 501: 58-62

发育中的大脑和成人大脑中都表达拓扑异构酶，而一些ASD患者的这种酶发生突变。然而，拓扑异构酶通过哪种机制来影响ASD，目前还不清楚。作者利用转录组测序以及神经元中RNA聚合酶II密度的全基因组定位，发现在敲除神经元的拓扑异构酶后，长基因的表达下降。作者指出，许多可信度高的ASD候选基因都特别长，但在TOP1抑制后表达下降。这种现象表明，拓扑异构酶可能普遍促进了ASD。

Illumina的技术：HiSeq 2000，TruSeq RNA，TruSeq，用于ChIP-Seq

Willsey A. J., Sanders S. J., Li M., Dong S., Tebbenkamp A. T., et al. (2013) Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell 155: 997-1007

近期的WES和WGS研究已经鉴定出九个可信度高的ASD基因。这项研究将Illumina的WES和RNA-Seq数据融合成共表达网络，研究了这九个基因对常见表型的贡献。作者解释了这些网络将如何指导未来的ASD研究，它们表明哪些基因最可能有重叠的分子、细胞或回路水平的表型。

Illumina的技术：HiSeq 2000，Genome Analyzer

Yu T. W., Chahrour M. H., Coulter M. E., Jiralerspong S., Okamura-Ikeda K., et al. (2013) Using whole-exome sequencing to identify inherited causes of autism. Neuron 77: 259-273

Steel综合征是一种发育的结构失调，1993年在波多黎各的23名西班牙裔儿童中首次发现。这篇论文介绍了对一个家庭的基因组分析，这个家庭有两个患病的兄弟姐妹。作者利用Baylor医学院人类基因组测序中心（BCM-HGSC）设计的全外显子组测序，对患病的儿童及其父母、另一个患病的表亲及其未患病的父母进行测序。通过分离来过滤检测到的遗传变异，作者发现了一个与疾病分离的纯合错义突变。这个变异破坏了胶原蛋白基因COL27A1，它编码软骨发育时表达的一种蛋白质。

Illumina的技术：HiSeq 2000，HumanOmniExpress

模式系统

神经系统疾病的建模一直颇具挑战性，这主要有两方面的原因：这些疾病患者的原代脑组织极其有限，以及这些疾病的多基因性。传统的敲除模型只重现了一部分的疾病表型，让人们去猜测研究结果与真正疾病之间的相关性。如今，三敲除小鼠、转基因大鼠和干细胞作为体外模型的引入大大拓宽了研究人员的工具库，并向“假想的”理想疾病模型更进一步。[231]开发充足的模式系统，对开发准确的诊断和治疗策略来说至关重要。

动物模型

精神分裂症和ASD的动物模型的开发也很有挑战性，因为90%以上的疾病是多基因的。因此，标准的单敲除小鼠模型只能在部分程度上模拟疾病表型。引入的突变只与疾病挨点儿边，而在动物身上观察到的症状可能代表了这个谱系中的其他疾病。[232]另一个难题是与症状的识别和定量相关：动物行为模式与人类不同；因此，解释动物的行为改变、感觉和意图可能是非常主观的。

> “考虑到与精神分裂症相关的等位基因有着低外显率，并且能够促成不同的疾病，将一个甚至几个等位基因插入动物模型中，可能产生不明确的表型，甚至根本没表型。” Hyman 2014

精神分裂症

对于精神分裂症和ASD研究，啮齿动物是最常用的模型。直到最近，这些模型也仅限于小鼠，不过现在也出现了一些敲除的大鼠。[233]大鼠比小鼠更有用，因为它们是高度社会性动物，拥有丰富的声通讯系统（包括超声波范围的频率），与人类的神经过程更为相似。[234]此外，临床前的毒理学研究通常在大鼠身上开展；因此，这些动物作为研究模型，能够大大简化药物开发过程。[235]

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人们利用三种传统方法中的一种，已经开发出精神分裂症的一些小鼠模型：传统基因靶向、条件基因靶向，或通过化学诱变剂进行点突变。[236]然而，这些技术产生的表型与精神分裂症几乎完全不同。基于这个原因，人们使用基于Cre/loxP的染色体改造技术来产生一些反映复杂基因组重排的模型，如大的缺失、倒位和重复。[237]

精神分裂症的最古老模型之一是精神分裂症1（DISC1）基因的显性失活突变。DISC1小鼠不仅适用于精神分裂症的研究，也适用于精神分裂症和药物滥用疾病的双重诊断。[238]这个突变对大脑结构或功能的影响仍有待研究。[239]

自闭症谱系障碍

小鼠模型让ASD疾病的基本原理得以证明。多个基因带有突变的小鼠敲除模型正大大促进人们了解疾病是如何发生的。这些基因包括SHANK3（Phelan-McDermid综合征，特发性ASD）、MeCP2（Rett综合征）、脆性X染色体（FMR1）、PTEN（自闭症）等。[240,241]SHANK3是一个很好的例子，说明了重现这个突变的确切类型和突变点的重要性：这个基因中的一些突变也与其他疾病相关联，包括精神分裂症和智力障碍。[242,243]SHANK3的微重复还与儿童的发育迟缓和畸形特征相关联。[244]这种现象突出了有必要使用基因组分析工具来准确鉴定谱系障碍中的突变，并验证它们在动物模型中的准确重现。

ASD的其他模型包括非人类的灵长动物、鸣禽、斑马鱼、果蝇和秀丽隐杆线虫。非人类的灵长动物有助于研究这种疾病的行为模式，因为它们负责调控社会行为的神经回路在解剖上与人类非常相似。[245]与人类一样，它们也拥有镜像神经元，这些细胞负责重复其他动物的动作，在自闭症中通常受损。基于伦理原因，在灵长动物中引入遗传突变目前还不可行。

鸣禽也作为模式动物，因为它们有一套发育完善的发声机制。与人类一样，发声学习是这个物种语言中的一个重要元素，而ASD患者往往受损。[246]此外，斑马鱼，果蝇和秀丽隐杆线虫也被广泛使用，以研究精神疾病的遗传基础。[247]

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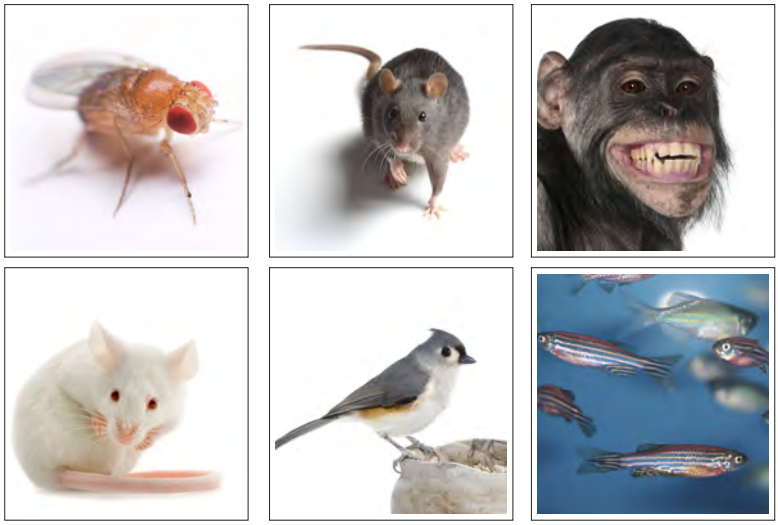

精神和神经退行性疾病的研究中常用的动物模型：小鼠、大鼠、非人类的灵长动物、果蝇、鸣禽和斑马鱼。

阿茨海默病

开发AD的动物模型相当困难，因为自发的淀粉样变性在实验室动物中不常见。衰老的非人类灵长动物可形成ß-淀粉样变性和tau纤丝内含体；然而，这些动物不形成人类AD的那些临床症状。[248]目前常用的AD动物模型主要限于遗传改造的小鼠。[249]这些模型能够成功模拟大部分的人大脑淀粉样变性，包括ß-淀粉样变性和tau病变。[250] 在所有病例中，人淀粉样蛋白的过表达都是必需的。[251]

过表达β-淀粉样蛋白的小鼠模型已经建立。尽管这些小鼠的大脑中不产生神经纤维缠结，但tau病变仍然可以观察到，因为ß-淀粉样蛋白病变激活了激酶，下调了磷酸酶，破坏tau降解。[252]与tau突变的小鼠相比，APP和tau同时突变的小鼠表现出更多的神经纤维缠结，从而表明ß-淀粉样蛋白积累在tau病程发展中的作用。[253]

除了上面提到的模型，目前还有与APP加工有关的基因敲除模型，如早老蛋白PSEN1和PSEN2以及β-分泌酶（BACE1）。不幸的是，这些模型都不能准确模拟疾病的所有主要症状和分子特征。具体来说，神经死亡的增加是这些症状之一，它似乎是选择和试验AD药物所必需的。将过表达APP的小鼠与表达突变的PSEN1或PSEN2的转基因动物杂交，获得了一个更先进的模型，并加入了第三种转基因（突变tau）。这些小鼠的特点是β-淀粉样蛋白病变加速、神经纤维缠结形成、神经元损失和认知减退，以及tau病变254。[254]

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尽管在开发AD的小鼠模型上已经取得了重要进展，但现有的模型并没有考虑LOAD中共有的免疫学因素的遗传和表观遗传变化。近期NGS技术的进步有望加强这些模型的构建，对开发改善AD病情的药物是至关重要的。[255]

帕金森病

PD的发病机制还没有弄清楚，而现有的动物模型存在许多限制。尽管如此，它们还是揭开了一些基本机制，让人了解这种神经退行性疾病的分子和细胞基础。目前开发的大多数PD动物模型都是毒性模型，而不是遗传模型。在非人类灵长动物和啮齿动物中重复多巴胺能神经元死亡和纹状体多巴胺损失时，毒性（也称为药理学）模型，特别是基于神经毒素的模型，是最有效的。毒性模型的好处还包括它们适用于非人类灵长动物，它们的运动症状和神经元结构与人类非常相似。唯一的限制在于灵长类动物的大脑中缺乏经典路易体的形成。

PD的遗传模型则非常有限，其原因在于遗传组分对这种疾病的贡献低：只有5%-10%的PD病例是遗传的。在这种形式的PD中，最常见的突变是LRRK2（它编码的酶可能参与α-突触核蛋白磷酸化的调控异常）[256]、PINK1（PTEN诱导的激酶1）和Parkin（它参与泛素蛋白酶体系统）。这些基因之一被敲除的转基因小鼠只表现出部分的PD表型，如运动异常、线粒体和黑质纹状体神经传递缺陷等。[257]

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在这些单基因的转基因小鼠模型中，没有一个实现了大量的黑质纹状体退化。[258]目前也出现了多基因的转基因小鼠模型（敲除α-突触核蛋白和parkin或DJ-1，或同时沉默PINK-1、DJ-1和parkin），但它们与PD症状和表型的相关程度也很有限。[259]

最近开发出的单基因PD突变大鼠模型被认为优于小鼠模型。大鼠的神经回路与人类更相似，并且它们不像小鼠那样容易焦虑，这对评估行为模式很重要。带α-突触核蛋白突变的转基因大鼠没有重大的运动缺陷，但确实表现出明显的嗅觉缺陷。[260]由腺病毒载体驱动的LRRK2带神经元特异突变的大鼠表现出黑质多巴胺能神经元的渐进性退化。[261,262]

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干细胞模型

对于神经系统疾病的研究而言，最有希望的模型之一是来源于患者的iPSC。这些细胞含有ASD特有的分子改变，将允许在人类神经组织上直接检测新的治疗方法。[263]iPSC在动物模型上的使用为校正异常的突触形态和生理，甚至逆转有症状动物的行为改变提供了工具。[264]

人类iPSC一直作为PD研究的模型。[265]由于中脑中的多巴胺能神经元仅有部分最容易退化，故移植的干细胞必须与那些受退化影响的细胞相匹配。[266]

另一种干细胞模型已经用于ASD治疗的临床试验，那就是间充质干细胞（MSC）。[267]据报道，它们通过重建神经网络的整合、促进突触可塑性的恢复以及释放抗炎性细胞因子来改变ASD的症状。[268]

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大脑发育的缺陷可能导致神经精神疾病的发生。这项研究试图确定15q11.2缺失对神经发育的功能作用，作者利用RNA-Seq和SNP基因分型芯片，研究了诱导多能干细胞（iPSC）来源的人神经前体细胞（hNPC）。他们发现15q11.2中的一个基因CYFIP1的单倍型不足影响了放射状胶质细胞，导致它们在脑室区外的定位异常。

Illumina的技术：HumanOmni2.5S

Ryan S. D., Dolatabadi N., Chan S. F., Zhang X., Akhtar M. W., et al. (2013) Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1alpha transcription. Cell 155: 1351-1364

之前有报道称PD和线粒体毒素暴露之间存在着关联。在这项研究中，作者利用干细胞模型来鉴定毒素的反应，采用Illumina的BeadArray开展基因表达分析。作者发现了一个通路，其中基础和毒素诱导的氮化/氧化应激导致转录因子MEF2C的S-亚硝基化。他们发现这些改变促使线粒体功能失调和凋亡性细胞死亡，表明这是PD的机制和潜在治疗靶点。

Illumina的技术：Human Gene Expression BeadArray

Zhang Y., Schulz V. P., Reed B. D., Wang Z., Pan X., et al. (2013) Functional genomic screen of human stem cell differentiation reveals pathways involved in neurodevelopment and neurodegeneration. Proc Natl Acad Sci U S A 110: 12361-12366

生物学

由于遗传和表观遗传突变的出现，神经和神经退行性疾病发生并且发展。然而，许多突变是体细胞突变（非遗传），受到生物学因素的影响，如免疫活性、肠道微生物组活性和环境因素。长期以来，这些因素在多细胞和单细胞水平的贡献仍然是假说，并充满争议。不过，如今高分辨率测序技术的出现能够揭开这些机制以及它们对疾病的贡献。

免疫力

过去，人们一直认为免疫系统是独立于中枢神经系统（CNS）的，但现在却承认它对CNS的正常功能以及多种神经系统疾病有重要贡献。[269,270]例如，对于PD，炎性细胞因子的水平升高与更严重的疾病形式相关联，如伴随着痴呆的PD。[271]对于AD，两项最大型的GWAS分析表明，与AD、胆固醇代谢和免疫应答相关的通路在疾病相关基因上有明显的重叠。[272]对于精神分裂症，许多免疫基因被确定是与疾病相关的遗传风险因素。[273,274,275]至于自闭症，持续的炎症被认为是疾病的共同因素之一。有意思的是，一些自闭儿童的发烧与他们社会行为的改善存在关联，为炎症参与症状谱打下基础。[276]

> “炎症和氧化应激往往都随着年龄的增加而增加，与多种慢性疾病存在关联。它们与神经退行相关，并被认为是可能促进精神分裂症的因素。” Anthes 2014

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血脑屏障阻止许多类型的免疫细胞渗透进大脑；然而，某些数量很少的免疫细胞，如树突状细胞和小胶质细胞，仍存在于大脑中，并促进死神经元的清除。[277,278]神经退化往往伴随着小胶质细胞和单核细胞在淀粉样斑块和濒死神经元周围的积累。[279]根据PD起源的一种假说，PD中多巴胺能神经元的死亡本身可能是由神经炎症促进的。[280]神经元及周围的胶质细胞被病毒感染，如日本脑炎病毒（JIV），使得神经元更容易受各种因素攻击，如衰老、氧化应激、环境应激和遗传倾向。[281]此外，神经元表达一些通常被认为属于免疫系统的分子，从而揭示了神经元和免疫系统之间错综复杂的相互作用。[282]

免疫治疗被认为是最有希望的治疗神经系统疾病的方法之一。celecoxib的治疗就是个例子，这种环氧酶2的抑制剂已在四项研究中证明对精神分裂症的症状有所改善，[283]还有ß-淀粉样蛋白的抗体，它作为去除致病性的β-淀粉样蛋白斑块的药剂，已经用在多项试验中，甚至到了III期临床试验。[284,285]

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精神分裂症是一种遗传性很高的疾病，但遗传可能性不表现为单基因效应。在这个迄今为止最大型的精神分裂症GWAS中，作者利用SNP芯片来分析36,989个病例和113,075个对照，以确定疾病的遗传风险因素。他们发现明显的遗传关联并不是随机分布在基因组中，而是集中在大脑表达的基因以及与典型的共病诊断（如ASD和智力障碍）相关联的基因。有意思的是，关联也集中在与免疫力相关的基因，这符合精神分裂症存在免疫失调的假说。

Illumina的技术：Human1M，HumanOmni2.5，HumanOmniExpress，HumanHap550，Human610，HumanHap650Y，HumanHap300

元基因组学

元基因组学指的是对无法在实验室中培养的多种微生物中获得的DNA进行研究。人类携带的细菌数量比人类细胞多10倍，而细菌基因比人类基因组多100倍。[286]新一代测序技术能对数千种生物进行平行测序，被证明特别适合这个应用。近期的技术进步让人们能够对来自环境样本或临床标本的单个微生物进行几乎完整的基因组组装，而不需要培养。[287]序列信息的积累已大大扩展了人们对微生物群体动态性质的认识，以及它们对环境和人类健康的影响。有了这组非凡且强大的测序工具，难怪元基因组学已成为发展最快的学科之一。

脑肠轴的概念在最近发展起来，强调了元基因组对心理过程的影响。研究表明，肠道微生物组在抑郁、焦虑、肠道易激综合征和神经系统疾病（如自闭症[289,290]和精神分裂症[291]）中发挥意想不到的重要作用。肠道微生物产物可能通过染色质可塑性来发挥对大脑的影响，这导致神经元转录的改变。[292]Hsiao等人提出用微生物组介导的疗法来治疗神经发育疾病。[293]

有意思的是，一些肠道细菌（定义为益生菌）对心理健康有积极影响，可以促进大脑活动。[294]这些活的微生物产生神经活性的物质，如γ-氨基丁酸和血清素，不仅对健康个体有好处，对精神疾病患者也有好处。[295]

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Stilling R. M., Dinan T. G. and Cryan J. F. (2014) Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. Genes Brain Behav 13: 69-86

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微生物暴露和性激素对自体免疫性疾病有很强的影响。这项研究以非肥胖糖尿病（NOD）小鼠为模型，调查了早期的微生物暴露对性染色体水平和自身免疫疾病的影响。作者利用16S rRNA Illumina测序鉴定出微生物组。通过比较雄性和雌性小鼠的影响，结果表明对于疾病遗传风险高的动物，早期肠道微生物组的改变强烈抑制了自身免疫。

Illumina的技术：MiSeq

Maurice C. F., Haiser H. J. and Turnbaugh P. J. (2013) Xenobiotics shape the physiology and gene expression of the active human gut microbiome. Cell 152: 39-50

大家都知道人类肠道微生物组中的微生物能影响肠道健康，但并不清楚它们对外源性物质代谢的影响，包括抗生素和药物。在这项元基因组学研究中，作者发现多种细菌的外源性物质响应基因参与了各种代谢和应激响应通路。结果表明，外源性物质可能对人类肠道微生物组具有重要意义。

Illumina的技术：HiSeq测序16S rRNA基因的V4区域

Schloissnig S., Arumugam M., Sunagawa S., Mitreva M., Tap J., et al. (2013) Genomic variation landscape of the human gut microbiome. Nature 493: 45-50

在不同时间间隔采样的个体表现出SNV模式的个体和时间稳定性，但是其肠道菌群的组成有相当大的改变。这种现象表明，个体特异的菌株并不能轻易替换，且个体可能有独特的元基因组基因型，这有望被个性化饮食或药物所利用。

Illumina的技术：Illumina read来自欧洲MetaHIT研究[296]和美国人类微生物组计划[297]

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环境因素

一般认为，暴露于微生物[298,299]以及暴露于各种工业的和农业化学品（特别是农药）会导致多种疾病的风险升高，其中包括神经退行性疾病。环境中的农药作为线粒体毒素，诱导硝化应激，抑制肌细胞特异的增强因子2C（MEF2C）的活性。这个因子参与了心脏形态发生、肌生成和血管发育。反过来，MEF2C又抑制了过氧化物酶体增殖活化受体γ辅助活化因子1α（PGC-1α）的表达，从而抑制了这种转录活化剂的神经保护功能。[302]

神经退行性疾病，包括PD，往往伴随着代谢疾病。例如，2型糖尿病可能刺激PD的发展。[303]Sekiyama等人表明，基因组研究可帮助人们更好地了解这种相互作用的机制，并开发出新治疗方法的策略。[304]

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单细胞

每种类型的细胞都有独特的谱系和功能，这有助于组织、器官以及最终的生物体发挥功能。每种细胞的谱系和发育阶段决定了它们之间如何响应，以及如何响应环境。尽管在细胞水平上全面了解组织的最终目标仍未实现，但近期单细胞分析的进步让人们可一窥未来。

最近一项对脑组织中的单细胞和神经元的研究发现，正常脑组织中的大多数（95%）神经元都是整倍体。不过，一名半侧巨脑症（HMG）患者因染色体1q上带有体细胞CNV，意外发现20%的神经元存在1q四体异常。这种现象表明，少数细胞中的CNV可能导致广泛的大脑功能异常。[305]这种复杂性只能通过单细胞测序方法来分辨。

最近的研究进展也强调了单个神经元的镶嵌基因组，展示了组成大脑特定区域的细胞之间的CNV。[306]即使大脑中的遗传变异在胎儿发育期间发生，[307]这种镶嵌的功能相关性到目前仍不清楚。人们不仅有兴趣探索镶嵌对于正常大脑的意义，还有意研究它在神经系统疾病和心理疾病中的作用。[308-311]

研究也开始阐明镶嵌性，在这里细胞间的异质性在基因组水平上是显著的。如果镶嵌存在于单细胞的遗传代码中，[312]那么蛋白表达、表观遗传变化[313]以及RNA异构体[314]都可能存在差异。单细胞测序为收集到的数据提供了一幅更完整的图像，有助于解释大脑特定区域中的镶嵌对单个细胞表型的影响。[315,316,317]

NGS的高度准确和特异使其特别适合单细胞和低水平的DNA/RNA测序。不断发表的技术正用于DNA突变、CNV、DNA-蛋白结合、RNA剪接的检测，以及RNA表达值的测定。

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那些依赖从细胞混合物中提取出RNA的测序方法不能反映出同一组织中不同细胞的表达差异。在这篇论文中，作者介绍了适用于单细胞研究的体内转录组分析（TIVA）。与Illumina测序技术相结合，作者捕获体外和体内的单个神经元并分析了转录组差异。此外，这种方法是非侵入性的，也许适用于完整组织。它将实现复杂组织中细胞异质性的详细研究，这在过去是无法做到的，并有望与活体功能成像结合使用。

Illumina的技术：670k BeadChip Array

Young G. T., Gutteridge A., Fox H. D., Wilbrey A. L., Cao L., et al. (2014) Characterizing Human Stem Cell-derived Sensory Neurons at the Single-cell Level Reveals Their Ion Channel Expression and Utility in Pain Research. Mol Ther 22: 1530-1543

由于缺乏感觉神经元细胞系，对疼痛的研究一般是在动物模型上开展的。在这篇论文中，作者展示了人类干细胞来源的感觉神经元，并结合群体和单细胞技术来开展详细的分子、电生理和药理的表型分析。他们监控定向分化长达六周，并利用Illumina的BeadArray来鉴定基因表达。作者表明，干细胞来源的神经元在分子和功能上都与来源于成熟背根神经节的人类感觉神经元相当。

Illumina的技术：BeadArray

Lister R., Mukamel E. A., Nery J. R., Urich M., Puddifoot C. A., et al. (2013) Global epigenomic reconfiguration during mammalian brain development. Science 341: 1237905

DNA甲基化参与了哺乳动物的大脑发育，以及认知和记忆背后的可塑性。这篇论文报道了人和小鼠额叶皮层在整个生命周期内的基因组组成、图案、细胞特异性以及DNA甲基化的动力学，分辨率达到单个碱基。他们在Illumina HiSeq上通过ChIP-Seq开展全面的甲基化组分析，揭示了单碱基分辨率的甲基化图谱。

Illumina的技术：TruSeq RNA, TruSeq DNA, HiSeq

McConnell M. J., Lindberg M. R., Brennand K. J., Piper J. C., Voet T., et al. (2013) Mosaic copy number variation in human neurons. Science 342: 632-637

对于每个物种的基因组，不仅个体之间有不同，母细胞和子细胞之间也有差异，因为错误的存在以及细胞分裂后DNA物质不均匀分布。到目前为止，同一个体的体细胞之间的遗传差异程度仍然未知。随着单细胞测序的出现，人们能够探索同一组织内各细胞之间的差异。在这项研究中，作者利用Illumina全基因组范围测序研究了单个神经元细胞中的CNV。他们发现，即使是同一组织的神经元细胞，CNV也是大量存在的。

Illumina的技术：Genome Analyzer$_{IIx}$, MiSeq, Nextera DNA Sample Prep Kit

Pan X., Durrett R. E., Zhu H., Tanaka Y., Li Y., et al. (2013) Two methods for full-length RNA sequencing for low quantities of cells and single cells. Proc Natl Acad Sci U S A 110: 594-599

通过RNA-Seq开展的基因表达谱分析是一种强大的工具，可了解特定组织的分子活性。然而，组织内基因表达的异质性分析需要RNA-Seq技术能够管理单细胞量的起始RNA。这项研究介绍了两种方法：基于Phi29 DNA聚合酶的mRNA转录组扩增（PMA）以及基于半随机引物PCR的mRNA转录组扩增（SMA）。两种技术都能与Illumina测序结合，对低起始量的RNA进行表达检测。这两种实验方案都实现了令人满意的高丰度mRNA检测/覆盖，即使是单个细胞。

Illumina的技术：HiSeq

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