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Molecular Neurology
分子神经病学

Stephen G. Waxman

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导　读

《分子神经病学》（*Molecular Neurology*）是从分子水平系统描述神经病学的一本专著，向读者充分展示了分子神经病学相关的基本原理和多种病征，系统介绍了该领域的有关概念、研究策略和最新进展，由国际知名的神经病学专家 Stephen G. Waxman 教授主编而成。Waxman 教授（Stephen. Waxman@yale. edu）于 1986 年加入哈佛大学，目前担任耶鲁大学医学院神经科学与再生研究中心主任（http://info. med. yale. edu/neurol/pva-epvacenter/info/center. html），长期从事脑与脊髓损伤后的功能恢复研究，研究领域涉及普通神经病学和多发性硬化等，在痛觉相关钠离子通道研究等方面取得一系列突出成绩，在 *Nature*、*Trends Neurosci*、*PNAS*、*J Neurosci*、*Brain*、*Neurology*、*Ann Neurol*、*Pain* 等国际权威期刊发表了 110 余篇高水平学术论文，是神经损伤与修复保护研究领域的国际知名科学家。Waxman 教授早已为国内广大读者所熟悉，此前由人民卫生出版社出版的英文原版教材《神经解剖学纲要》（*Correlative Neuroanatomy*，2001）和《临床神经解剖学》（*Clinical Neuroanatomy*，2002，25th edn）均为 Waxman 教授的代表作品，被列为神经解剖学和神经病学相关专业研究人员和研究生的推荐参考书目。他同时还出版了 *Multiple Sclerosis as a Neuronal Disease*、*Form and Function in the Brain and Spinal Cord*：*Perspectives of a Neurologist* 等系列专著，系统总结了自己从事脑和脊髓形成及功能研究长达 30 余年的科研成果。

在“神经病学”研究领域，国内已有较多专著，据其内容大体可分为三类。①针对神经系统疾病进行详细而全面的介绍，如王维治主编的《神经病学》、刘焯霖编著的《神经遗传病学》、陈清棠主编的《临床神经病学》等；以及面向医学院校学生的系列教材，如姜亚军等主编的《神经病学》（高等医学院校教材）、贾建平主编的《神经病学》（5 年制全国高等医学院校教材）等。均较多偏向临床方面的研究内容，通常涵盖神经系统常见疾病的临床表现、辅助检查、诊断及治疗等，部分专著涉及某些神经系统疾病的分子基础、诊断与治疗进展、新药与新技术等，总体上体现出“以病为主”的写作指导思想。②深入介绍神经系统疾病研究的某一方面，如肖军主编的《神经病诊断学》和李茂绪等主编的《神经系统疾病实验室诊断学》重在介绍神经系统疾病的诊断原理和诊断技术，韩春美主编的《神经精神病学》突出神经精神疾病的概念、原理、诊断和治疗，韩仲岩等主编的《神经病治疗学》则突出神经系统疾病的治疗研究，总体上体现出“突出侧面”的写作特点。③第三类是神经病学研究所需的实验技术等方面，着重介绍神经病学研究领域的关键技术，如刘新峰等主编的《实验神经病学》突出介绍多种神经系统疾病的实验动物模型，郭云良等主编的《神经病学实验技术》突出描写神经病学研究的多种实验技术，体现出“以技术为主”的指导思想。以上三类基本上覆盖了神经病学研究领域的各个方面，但均无类似于本书突出“以分子水平为主”的写作风格，因此对于国内神经病学研究领域而言，Waxman 教授编著的《分子神经病学》一书的引进出

版对于国内神经病学研究领域是一个重要补充，为国内从事临床神经病学的科研工作者提供了了解这些疾病分子基础的崭新窗口，也为从事神经生物学研究的科研工作者提供了分子水平变化在神经系统疾病的“异常表型”。相信本书的出版一定会加速推进国内神经病学的研究从临床深入到基础水平，惟其如此方能更好地为临床上进行多种神经系统疾病的防诊治服务。

本书共包括十一部分内容，分为34章。第1章中，作者首先从遗传学、基因表达调控、遗传多样性和遗传性疾病等角度入手，重点介绍了神经系统遗传性疾病以及非孟德尔遗传模式的遗传性疾病；还介绍了疾病相关基因的研究策略，包括分子诊断中的PCR技术、基因突变和分类鉴定等；最后讨论了遗传性疾病的有关治疗问题，包括酶替代疗法、基因疗法、RNA干涉及基于小RNA的治疗策略等，这些已陆续为神经病学这一经典领域注入新的活力。

第2章的主题是神经病学与基因组医学（注意此处不是“遗传医学”——这一概念更加突出了分子神经病学的特点）。作者先后介绍了基因组的一些相关内容，包括人类基因组计划（HGP）及单倍体型计划（HapMap）等。本章内容十分简明扼要，主要包括单基因疾病及复杂性疾病（多样性）、疾病易感基因的鉴定、神经病患者的家族史、药物遗传学、基因之间及基因与环境之间的相互作用、基因表达水平的调节机制、剪接变体、小RNA等。作者还进一步介绍了比较基因组学，其中描述了生物信息学、蛋白质组学等一些重要内容。本章最后涉及了线粒体和线粒体DNA的一些知识——后者在大量神经系统退行性病变中尤为重要。

与第2章相对的是，第3章重点描述了线粒体功能及线粒体在神经系统中的功能紊乱。在介绍线粒体的正常结构与功能的基础上，进一步对线粒体遗传学、生物能量生成和钙信号进行了叙述，对线粒体蛋白输入和线粒体分裂与融合以及线粒体功能在神经系统中的特化等进行重点介绍。与此相对应的是，线粒体功能异常对于神经细胞死亡和神经系统疾病的影响显而易见，诸如ATP生成水平下降、线粒体分布异常、自由基生成失控、钙超载与兴奋性毒性、蛋白进入线粒体异常、凋亡过程中线粒体功能的变化等均有介绍。因此，神经退行性病变中线粒体的功能紊乱这一作用方式并不奇怪。这一章内容凸显了线粒体的重要性——当然，正因为线粒体功能如此重要，显然其一旦失控则可导致神经系统出现严重疾病。

第4章描述了神经通道和受体这两类重要的功能分子，包括电压门控的离子通道和配体门控的离子通道的结构和功能及其重要生理作用。本章还进一步叙述了离子通道异常导致的神经病，例如癫痫、共济失调、偏头痛、疼痛、过度惊吓症、肌强直与周期性麻痹等。

作为重要的共性问题，作者显然意识到蛋白质折叠的重要性，因此第5章重点介绍了神经系统中的蛋白质折叠异常、分子伴侣网络及热激应答等重要而又基本的分子调节过程。其中主要叙述了热激蛋白（HSP）家族中HSP70、HSP40、HSP90、HSP60及HSP100蛋白家族成员以及小HSP家族成员的相关知识。它们对于分子伴侣机器的正常工作举足轻重，后者显然与神经系统的生理和病理状态相关。在此基础上，作者还进一步叙述了热激应答相关的分子伴侣表达等内容，包括作为转录因子的热激因子（HSF）家族及其调节。作者还进一步叙述了神经退行性病变中分子伴侣的作用，包括

多聚谷氨酰胺（polyQ）疾病、帕金森氏症（PD）模型等，这些从总体上体现了分子伴侣的重要性。当然，从治疗角度而言，针对分子伴侣异常进行治疗的研究目前正在快速推进中。

由于脑代谢性功能检查是神经病学中的一个重要方面，因此第 6 章较为系统地叙述了磁共振波谱技术（MRS）、磷酸肌酸回路假说、ATP 和磷酸肌酸合成的磁化传递测量、氢质子光谱、碳光谱、脑皮质乳酸的磁共振光谱测量、星形胶质细胞-神经元乳酸穿梭假说、脑皮质的氨代谢假说等内容，其中涉及这些用于检测神经系统功能性障碍的技术原理以及与脑电异常相关的分子依据。

第 7 章所介绍的神经病学研究中的基因治疗策略也是十分重要的内容。本章较为详细地介绍了基因治疗的基本知识及应用，内容涉及病毒载体和非病毒载体两大类，对逆转录病毒、腺病毒及腺相关病毒和疱疹病毒予以着重介绍，为读者提供了丰富的信息。作者重点讨论了其中的共性问题——载体的靶向性和靶基因表达的调节问题，以及中枢神经系统和外周神经系统疾病治疗中病毒载体的应用现状，和多种人类中枢神经系统疾病的基因治疗。还进一步介绍了靶向肌肉的基因治疗问题，因为其中也涉及到一些神经功能异常，如杜氏肌营养不良等。这显然是接近于临床应用的一个新方向。

第 8 章叙述了程序性细胞死亡（PCD）及其在神经病学中的作用。先后介绍了程序性细胞死亡的基础知识、当前研究进展、发生原因及其分类等内容。显然，PCD 在神经退行性病变中起了重要作用，在一定程度上可以纳入神经系统疾病考虑之中，虽然这已经是疾病发展晚期的情况了。不过有意思的是，神经干细胞对于神经退行性病变的应答（死亡和复兴）也已引起重视，对于抑制 PCD 的发生具有一些积极作用。接下来的第 9 章从分子水平对发育神经病学进行了系统描述，虽然仅有短短三页纸篇幅，但为读者了解神经病学的纵向进展提供了重要参考。随后的第 10 章对神经系统的代谢性疾病进行了叙述，其中包括糖转运体 I 型缺陷、门克斯病（又称“钢发综合征”）、多巴反应性肌张力障碍疾病、丙酮酸代谢紊乱、糖基化紊乱、有机酸尿症、尿素循环代谢障碍、半乳糖血症、苯丙酮尿症、莱施-奈恩综合征、泛酸激酶缺陷、Smith-Lemli-Opitz 综合征等，为读者提供了丰富的信息。神经肌肉发育的遗传学紊乱也是作者叙述的一个重点，其中介绍了发育过程中运动控制及调节系统的形成与功能化过程、神经-肌肉系统的结构与功能及其异常，尤其是发育过程中神经肌肉接头的功能紊乱，如胆碱乙酰化酶（ChAT）缺陷、乙酰胆碱受体（AChR）缺陷、受体相关蛋白（rapsyn）缺陷、慢/快通道综合征、乙酰胆碱酯酶（AChE）缺陷等。本章同时还提供了其他诸如肌肉钠通道和兴奋性的遗传紊乱、Andersen 综合征中钾通道突变、RNA 剪接异常和肌强直营养不良等资料，为了解发育紊乱提供了丰富信息。

鉴于脑血管疾病具有发病率高、病死率高和致残率高的特点，本书第三部分系统地讨论了脑卒中和脑创伤的相关内容，其中包括三章内容，分别叙述了缺血性脑疾病的分子机制、出血性脑病和创伤性脊髓损伤的分子和细胞治疗前景。在缺血性脑损伤方面，作者叙述了缺氧/缺血、兴奋性氨基酸、自由基和炎症等在脑卒中中的作用，叙述了生长因子以及皮质缺血时的基因表达特点，同时还包括了细胞凋亡等内容，为读者了解脑卒中的分子事件提供了充分的资料。与此相对应的是，在出血性脑病方面，书中先后介绍了血管生成的相关知识及孟德尔类型遗传类型的出血性脑病、原发性出血性脑疾病

（血管损伤所致）等，后者包括颅内动脉瘤、多囊肾动脉瘤、烟雾病、脑海绵状血管瘤、遗传性出血性毛细血管扩张等。在继发性出血性疾病方面，介绍了遗传性脑淀粉样血管病和凝血功能紊乱。本部分最后，作者对创伤性脊髓损伤中的分子紊乱治疗中的崭新前景进行了描述，包括流行病学、预后和病理学等方面的内容。在影响轴突再生方面，作者叙述了其中不利于再生的因素，如髓鞘相关抑制剂、胶质瘢痕与硫酸软骨蛋白多糖、cAMP、RhoA 等。基于细胞的治疗对脊髓损伤提供了新的内容，如嗅鞘细胞（OEC）的应用为患者带来了新的曙光。脊髓损伤后的分子适应性调节是随后发生的事件，对于疾病的治疗转归具有积极的促进作用。本部分末叙述了未来研究的趋势，并指出这些研究对于提高患者的生存质量具有重要意义。

退行性疾病历来是神经病学研究领域的重头戏。第四部分（共八章内容）对此进行了叙述，其中包括帕金森氏症（PD）、阿尔茨海默氏症（AD）、包括亨廷顿舞蹈症（HD）在内的多聚谷氨酰胺紊乱、Friedreich 氏共济失调及其 DNA 功能缺失相关紊乱、肌张力异常疾病、运动神经元疾病——肌萎缩性脊髓侧索硬化症、自主神经系统遗传紊乱、作为神经退行性病变的多发性硬化等内容。与此领域其他专著不同的是，本书侧重从分子角度对此类疾病进行描述，包括其分子机制、疾病模型中的分子水平异常（如磷酸化异常、泛素化异常等）、治疗的分子水平依据等，对其中存在的共性分子问题进行了较为全面的阐述。

神经系统功能活动的重要特点在于兴奋性。神经冲动的发起与传递过程出现异常必然导致疾病的发生，因此，第五部分叙述了后天性癫痫的细胞和分子机制。在癫痫方面，首先介绍了用于实验研究的模型，然后对嗅叶癫痫进行了阐述，包括其中的基因表达谱、细胞形态学、突触发生、神经发生、神经递质系统——谷氨酸、γ-氨基丁酸（GABA）、电压门控系统、热性惊厥等。创伤和脑卒中后癫痫、Rasmussen 综合征、感染后癫痫等也有叙述。此部分还涉及退行性疾病癫痫的内容，作者指出多个基因导致惊厥，但其中仅有少量是惊厥基因，同时还指出对惊厥进行正确分型的重要性，因此在具体研究时需要综合、全面地进行考虑。作者还重点介绍了关于 Tourette 综合征（抽动障碍）的一些内容，包括临床症状描述、发展历史、共发生条件、流行特点、神经心理学发现、病因学和病理学及神经振荡等，为读者了解此方面内容提供了系统知识。

睡眠和生理节律的紊乱显然是神经病学中的经典话题。作者用了一章篇幅对其进行叙述，主要包括睡眠和生理节律对于个体的重要性、其异常表型和生物学机制，以及其中的一些基因（如时钟控制基因，CCG）和家族性提前睡眠期症候群的现象和分子机制等，为了解此方面的分子机制提供了一些参考信息。作者最后指出，睡眠是一个很重要的表型，也是将基因和行为学之间进行关联分析从而阐述其中分子机制的典型例子。

从分子角度而言，慢性疼痛也是一种分子（功能）障碍性疾病。第七部分介绍了不同表型的疾病，包括伤害感受过程中神经元的情况、伤害感知、痛觉的化学介导机制、机械感觉、热痛感受等，其中重点介绍了瞬时受体电位蛋白（TRP）家族、钾通道、钙通道和神经递质释放等内容。还包括小胶质细胞相互作用和慢性疼痛的关系，以及其中涉及的细胞因子受体 CCR2、P2X4 受体等内容。作者进一步将这些内容与脑功能成像等密切结合起来，为了解痛觉的分子机制提供了重要参考。偏头痛是另外一种典型例子，本部分对神经肽（如 VIP、CGRP）在其中的作用进行了描述，同时还介绍了一大

批家族性偏瘫型偏头痛（FHM）相关基因，对于了解偏头痛的分子事件提供了重要参考。

第八部分首先用一章篇幅介绍了腓骨肌萎缩症（Charcot-Marie-Tooth 病）的相关内容，其中重点介绍了外周髓磷脂 P0 蛋白（MPZ）与 CMT1B 等主要与髓鞘生成异常相关的蛋白，这些知识对于了解外周神经系统疾病的分子依据具有重要参考价值。

神经-免疫疾病无疑是另外一大类重要的神经病，作者用了三章内容对此进行介绍，分别包括多发性硬化中大量髓鞘病变、神经肌肉接头（NMJ）与运动神经末梢（MNT）的自身免疫疾病、遗传缺陷以及神经系统副肿瘤综合征等。作者对于其中引起自身免疫的分子进行了描述，但更多的内容是对疾病本身的描述及治疗方面。当然，NMJ 和 MNT 的情况更复杂一些，涉及到 ACh、AChR 及相关功能分子的复杂变化。在神经系统副肿瘤综合征方面，对分别由抗体介导的和由 T 细胞介导的疾病发展过程进行了叙述，其中涉及到诊断、症状、治疗等内容。

线粒体功能异常与多种神经病有关，因此，作者单列一章内容对其叙述，主要包括线粒体 DNA（mtDNA）突变致病和细胞核 DNA（nDNA）突变致病及其他 nDNA 突变，评价了其在影响呼吸链功能、基因组能量传递缺陷等方面的作用，对于了解和认识线粒体分子病所致神经病具有重要意义。

最后，本书介绍了 HIV-I 感染和艾滋病的分子神经病学，其中重点介绍了 HIV 相关痴呆的流行病和分子机制（如 IL-16、CxCR 等），重点介绍了细胞因子、HIV/gp120 等影响神经干细胞的情况以及巨噬细胞、小胶质细胞在其中的作用。分子机制方面，本部分的内容还涉及 Glu 受体、NMDA 受体等。基于这些内容所提出的治疗方案包括 Glu、细胞因子、红细胞生成素（EPO）等，对于 HIV 所致神经病的治疗具有一定促进意义。

总体而言，本书由该领域众多国际学者执笔撰写，内容既有宏观全面的综合性评述，又有细致入微的详细介绍，各章内容既有交叉、联系，又有重点区别，整体内容十分丰富，可读性强，非常适合于目前正从事和有志于从事神经系统疾病研究的科技工作者和临床工作者深入阅读。相信本书将激起志在学习和研究神经病学的分子基础、研发神经病的新治疗策略的广大读者的兴趣。由于本书非一人之力完成，因此各章节风格可能略有差异，但作为读者而言，如能通读全书，领略各章风格，博采众家之长，必然获益匪浅。

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前　言

从丹麦的奥胡斯到瑞士的苏黎世，全世界医学院校的学生都在认真学习神经病学的精华内容。其中的高年级学生在实践中面临挑战，每天需要面对众多陷入神经病困境的患者。实验室中的科学家们对于神经系统也很感兴趣，尤其是对于十分罕见的被认为具有神经病特点的疾病，由此也就界定了神经病学的研究范畴。那么，到底什么是分子神经病学呢？为什么我们需要这一学科？

经典意义而言，神经病学是首先基于神经系统的内在定位、其次基于病理学鉴定的一门学科，目前已经发展为针对神经系统疾病进行的系统而又缜密的诊断和分类系统。因此，数十年来，大多数神经病学家已经具有如下经验，即要求每个患者回答以下问题：哪儿不舒服？怎样不舒服？这一方式是经典神经病学进行后续分析的基础，被视为金科玉律而广为使用。高水平的神经病学家确实被其他专业的临床医生视为德高望重的疾病诊断专家。

然而，神经病学的治疗方面则相对历史较短。例如，30 年前，一些研究所的医学专业学生在上课时并未被告知去对多发性硬化的早期过程进行诊断，因为当时对此方面还所知甚少。脑卒中患者被告诫最好是卧床休息而并非进行其他治疗。类似地，在当时医生几乎无能为力的情况下，脊髓损伤患者则被告知没有康复的希望。

所幸的是，所有这些情况都已在大幅度改观。神经病学正处于创新发展的开始阶段，已经从虚无缥缈的感性诊断时代进入十分活跃的理性诊断时代。以往束手无策的部分神经病已有十分有效的治疗方法。一些新治疗方案的研究也已提上议事日程。

那么，为什么还要有分子神经病学呢？众所周知，药物的疗效是通过作用于靶分子实现的。靶分子的特异性越好，药物作用的特异性也就越高，副作用也就相应越少（事实上，新药研发过程中最大的困境就是新的候选药物存在难以接受的副作用）。分子神经病学正处于一个令人目不暇接的快速发展时期，无论在揭示神经病的病理机制还是病理生理机制方面均具有十分重要的作用，同时也可用于揭示可能的治疗靶标研究。

本书旨在为在读研究生或已获学位的硕士和博士生、研究人员、关注基础研究的临床科技工作者、从事神经科学和生物医学科学的研究人员提供与神经病学相关的基本分子医药知识。本书的目的并非在于为读者提供深奥难懂的信息或者企图成为百科全书，而是更倾向于展示与分子神经病学相关的基本原理和典型病例，揭示其概念、精华以及该领域的激动人心之处。在此框架下，本书的章节结构已能够体现出神经病学的总体轮廓，显示了神经病学从一个描述性的、基于解剖学的专业研究领域发展为基于机理的、分子水平概念的全新的研究过程。随着神经病学被融入更多的分子概念，毋庸质疑，众多神经系统疾病的治疗技术必将获得突飞猛进。

与今日相比，此后十年，神经病学将无可非议地大幅度实现诊断的特异性。这无疑预示着神经病学的发展历史将大踏步迈入分子层次。因此我们鼓励读者在阅读本书时，尽可能多从分子神经病学的角度思考神经病的治疗内涵，鼓励读者多思考神经病学的分

子层面，不仅仅基于我们目前的知识去理解，而且应该思考明天我们如何才能对公众所面临的神经系统疾病有所贡献。

Stephen G. Waxman, MD, PhD

（张成岗　译）

目　录

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1

Genetics as a Tool in Neurology

Dennis R. Johnson and Fuki M. Hisama

I. Introduction

Genetics is the study of heredity, and seeks to explain the mechanism of hereditary transmission, as well as the genetic basis of individual variation. Medical genetics is the science of genetically associated biologic variation relevant to human traits and diseases. In industrialized countries, improvements in public health and medical care have resulted in a marked reduction in mortality from infectious causes, or nutritional deficiencies; during this time, there has been a corresponding increase in awareness of the role of genetic factors in human diseases, including neurological disease.

Although genetic disorders sometimes have been perceived as rarely encountered outside of a tertiary medical center, this notion is no longer true. Although a particular genetic disease may be rare, defined as affecting fewer than one in 250,000 individuals, some genetic disorders such as spinal muscular atrophy and cystic fibrosis are common in the population, affecting from one in 500 to one in 1,000 people.

In aggregate, the thousands of single-gene disorders affect millions of people. The proportion of recognized genetic diseases has increased in both the pediatric and adult populations as our ability to identify and understand the role of genes in biology and medicine has increased. New genetic disorders continue to be described. In 1994, McKusick's Mendelian Inheritance in Man listed 6,678 monogenic human traits, and accessing the online version on September 6, 2006 showed 17,033 entries, including over 1,500 Mendelian traits with an unknown molecular basis (www.ncbi.nlm.nih.gov/OMIM). Many chronic disorders affecting the nervous system are genetically determined. In others, genetic risk factors increase the likelihood of developing certain diseases, but do not always result in the disease.

In the last 15 years, hundreds of human disease genes have been mapped and cloned because of the explosion of basic knowledge in genomics and molecular genetics. The identification of these genes has led to novel insights into disease pathogenesis in humans and model systems. A growing number of genetic tests are available on a clinical basis

to assist in the diagnosis of a symptomatic patient, to accurately predict risk to family members, and to assess the likelihood of a serious drug side effect. Sophisticated genetic methods are now being applied to the next genetic frontier: the challenging task of identifying genes contributing to common diseases such as Alzheimer's disease and schizophrenia. These genetically complex disorders are thought to arise from the cumulative effects of variants in several genes, in combination with environmental effects. The goal of this chapter is to provide an overview of the genetic principles that have transformed neurology into a molecular specialty.

II. Structure and Function of Genes and Chromosomes

A. DNA Structure and Replication

The information for the development of an organism and the specific functions of cells, tissues, and organs is stored in its DNA. The double helix structure of DNA was described a little more than 50 years ago (Watson and Crick, 1953). DNA is a nucleic acid composed of *nucleotide bases* (adenine (A), thymine (T), guanine (G), and cytosine (C)), a *deoxyribose sugar*, and *phosphate groups*. These components are organized into two sugar-phosphate strands of opposing polarity, and paired nucleotide bases. Each pair consists of a purine (guanine or adenine) and a pyrimidine (thymine or cytosine). Guanine pairs with cytosine via three hydrogen bonds, thymine and adenine pair via two hydrogen bonds. Every time a cell divides, its DNA must be replicated in the daughter cells. During the process of replication, the two strands of DNA separate, and each is copied by DNA polymerase. Thus, DNA replication is semiconservative, with each double helix consisting of a "new" and an "old" strand (Alberts et al., 2002).

B. Gene Expression and Transcription

The genetic information in DNA is transcribed into RNA in the nucleus, or in the case of a few genes, in the mitochondria, by means of a DNA-directed RNA polymerase; the RNA crosses into the cytoplasm where translation of the information into polypeptides occurs on ribosomes. Both post-transcriptional (RNA splicing, capping, and polyadenylation) and post-translational modifications (cleavage into a mature peptide, hydroxylation, phosphorylation, the addition of carbohydrate or lipid groups) may take place. The basic theme of unidirectional transfer of information from DNA®RNA®protein has been termed the *central dogma* of molecular biology (Alberts et al., 2002). Although the term reflects its near universal occurrence, there are exceptions to this important principle. Eukaryotic cells contain sequences that encode reverse transcriptases that enable making cDNA copies of RNA transcripts, which can then be inserted into the genome.

The vast majority of DNA is not transcribed. Only approximately 1.5% of the DNA in mammalian cells codes for proteins (Strachan & Read, 2004). The remaining noncoding DNA (formerly called "junk DNA" contains the intronic sequences within genes, various classes of highly repetitive DNA, nonfunctional copies of genes (pseudogenes) and noncoding RNAs. The potential role of noncoding DNA is the subject of considerable interest (Mattick, 2004).

C. Chromosomes

In eukaryotic cells, DNA is organized into chromosomes (Tyler-Smith & Willard, 1993). The correct diploid number of human chromosomes was determined to be 46 (Tijo & Levan, 1956). This includes 22 paired maternal and paternal autosomes, and a pair of sex chromosomes. During interphase, a chromosome consists of a single, extended DNA molecule and its closely associated histone and nonhistone proteins. The packaging of DNA is a dynamic, reversible, highly organized process that takes place on multiple levels and enables a 10,000 fold compaction of the DNA. The basic unit of packaging is the nucleosome, consisting of a core of eight histone proteins around which the DNA is coiled (Jenuwein & Allis, 2001). A string of adjacent nucleosomes are coiled into a chromatin fiber of 30 nm diameter, visible by electron microscopy. These in turn form a long looped chromosome segment.

With each cell division, the chromosomes become even more condensed, and the DNA content is replicated. The typical textbook image of chromosomes reflects a brief stage of the cell cycle, their most highly condensed state during metaphase, in which the chromosome has been replicated, and exists briefly as a two-chromatid entity.

The development from single-cell zygote to multicellular organism requires millions of cell divisions, which occur through the process of mitosis. The result of mitosis is the formation of two daughter cells containing identical genetic information. During mitosis, the chromosomes condense and become visible (prophase), the nuclear envelope disappears, and the chromosomes migrate to the equatorial plane (prometaphase). Importantly, during mitosis, the maternal and paternal homologous chromosomes do not pair during metaphase, in contrast to meiosis (discussed later). In anaphase, each centromere splits and the two chromatids of each chromosome migrate to opposite poles; in telophase, the chromosomes reach the poles, and the nuclear membrane reforms.

D. Meiosis

Meiosis is the specialized process of cell division by which gametes are formed. Somatic cells possess a diploid DNA content or two copies of the chromosome set. In humans, the diploid number of chromosomes is 46, including

the sex-determining X and Y chromosomes. Meiosis involves a single round of DNA replication, but two rounds of cell division; the products (spermatozoa or an oocyte) contain the haploid number of chromosomes (23 in humans). Meiosis differs fundamentally from mitosis in several respects. First, the products of mitosis are diploid, the products of meiosis are haploid. Second, in meiosis, the homologous chromosomes pair up. Third, genetic recombination arises from the exchanges between the homologous chromosomes (crossing over), a process that has proven important in positional cloning. Finally, the products of mitotic division are generally identical to each other, whereas the products of meiotic division differ genetically from one another due to the exchange of genetic information that occurs during crossing over.

Chromosomal abnormalities may affect human reproduction or cause recognizable genetic syndromes. Problems arising from chromosomal aberrations include infertility; fetal loss; gain or loss of complete chromosomes resulting in recognizable phenotypes such as Down syndrome (47,XX, +21), Turner syndrome (45,X), or other structural abnormalities such as deletion, insertion, inversion, duplication, translocation, or formation of a ring chromosome (ISCN, 1995; Shaffer & Tommerup, 2005). Although many chromosomal abnormalities cause a neurological phenotype, particularly mental retardation with or without epilepsy, they are often multisystem diseases and space does not permit detailed discussion. For further information, refer to Gardner and Sutherland, 1996. In the clinical setting, cytogenetic studies of human chromosomes are performed using accessible tissues: lymphocytes from blood, fibroblasts from skin biopsy, or fetal cells obtained by amniocentesis or chorionic villus sampling.

E. The Human Genome Project

The genome is the total sum of genetic material in human cells. The Human Genome Project (see Table 1.1) was based upon the central importance of DNA to understanding the function of genes, their role in human disease, and the potential for medical benefits. The Office of Human Genome Research was established in 1988, and the Human Genome Project originally was envisioned as a 15-year effort to produce high resolution genetic and physical maps leading to the sequence of the human genome as the primary goal. The Human Genome Project became an international project carried out in specialized genome centers with high throughput sequencing capability, and the ability to release the sequence to publicly available databases. Secondary goals included new technological developments in DNA sequencing tools and technology, bioinformatics, genome projects for several widely studied model organisms (*E. coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, and mouse), and the ethical, legal, and societal implications (termed ELSI) of human genome studies. Competition from a private company, Celera, and technical advances sped up the timeline of the project. In 2001, a draft of the human genome was released (2001; Lander et al., 2001), and the finished sequence of the human genome and the model organisms was available by 2003.

F. Overview of the Human Genome

The genome comprises 3,000 Mb encoding an estimated 35,000 genes compared with 18,425 genes in *C. elegans* and 13,601 genes in the fruit fly (Claverie, 2001). Organismal complexity, therefore, does not fully reflect genome complexity, and is incompletely understood, but could be explained by increased alternative splicing in complex organisms or perhaps by noncoding DNA.

Human genes vary in size from less than 1 Kb to the 2.4 Mb dystrophin gene. Although most protein coding genes possess introns, a few lack introns, including the dopamine D1 and D5 receptors. Because of the complexity of the human brain, over half of genes are thought to be expressed predominantly or exclusively in the nervous system. It is therefore not surprising that a number of neurological diseases have a genetic basis. Human genes are not evenly distributed on chromosomes. Instead, there are "deserts" devoid of genes (e.g., regions of heterochromatin), and "oases" of gene-rich regions. In general, the distinctive Giemsa staining pattern of light and dark bands observed on a karyotype reflect gene-dense and gene-poor regions, respectively.

G. Genetic Diversity: Normal Variation and Genetic Disease

Although the DNA sequence of any two humans is 99.9 percent identical, nevertheless, the degree of human genetic

Table 1.1 Internet Resources for Genetics

National Human Genome Research Institute	(www.genome.gov/)
Online Mendelian Inheritance in Man	(www.ncbi.nlm.nih.gov/Omim/)
Genetic Testing, Genetic Clinics and Gene Reviews	www.genetests.org
National Organization for Rare Diseases	www.rarediseases.org
National Coalition for Health Professional Education in Genetics	www.nchpeg.org
Human Genome Organization	www.gene.ucl.ac.uk/hugo
Human Gene Mutation Database	www.hgmd.cf.ac.uk
American Society of Human Genetics	www.ashg.org
National Society of Genetic Counselors	www.nsgc.org
American College of Medical Genetics	www.acmg.net
American Board of Medical Genetics	www.abmg.org

variation is remarkable, and readily detected by the casual observer. Genetic variation also influences the most common medical tests such as blood pressure, cholesterol, and glucose, as well as causes the development of diseases such as neurofibromatosis, familial Alzheimer's disease, certain forms of epilepsy, among others. Genetic variation may also affect the effectiveness or the predisposition to side effects of the conventional drugs currently on the market. A number of liver enzymes have polymorphisms that affect the rate of drug metabolism. For example, the CYP2D6 gene in the P450 cytochrome system affects the metabolism of many psychoactive drugs, including tricyclic antidepressants and atypical antipsychotics, so that a dose that causes toxicity in a patient with low enzyme activity may be nontherapeutic in a patient with high enzyme activity (Wolf et al., 2000).

All genetic variation arises from a change in the DNA sequence, termed a mutation. Mutations may occur in a somatic cell and be passed on to its daughter cells (a critical event in the development of many cancers) or a mutation may affect a germline cell (and thus be capable of transmission from one generation to the next). Mutations may be induced by exogenous agents such as ionizing radiation, ultraviolet radiation, various classes of chemicals such as alkylating agents, nitrogen mustard, and formaldehyde. Spontaneous mutations arise during the process of DNA replication that continues throughout an individual's lifetime. Efficient cellular DNA repair systems correct the vast majority of mutations, so that the normal mutation rate is low, but is not zero. The residual mutations may (1) be functionally neutral and thus clinically silent or associated with normal variation, (2) may result in disease, or (3) may provide some selective advantage that will provide a substrate for evolution.

The chromosomal location of a gene is its locus. The different, alternate forms of a gene are referred to as *alleles*. If an individual has the same allele on both the maternal and the paternal chromosomes, the person is homozygous. If the two alleles differ, the individual is heterozygous. The alleles present at a specified locus comprise the genotype. A locus in which two or more alleles have frequencies less than 1 percent of the normal population is termed a polymorphism.

III. Genetic Medicine

Genetics is the study of inheritance and *medical genetics* is the branch of medicine that specializes in inherited diseases (2006; McKusick, 1993). Neurogenetics, by extension, aims to identify and characterize the inherited components of neurological disease, and in so doing, contributes broadly to the elucidation of neurological disease mechanisms (Rosenberg, 2001). Clearly, ever more powerful contemporary molecular biological technologies and the availability of the sequence of the human genome have enhanced the potential yield of applying genetic approaches in the clinic. However, optimizing the outcome from the evaluation of a patient/family requires an understanding of a number of key concepts, strategies or approaches—the tools of clinical genetics. In addition, it may soon be possible to sequence an individual's entire genome at reasonable cost, thus opening the door to *genomic medicine* (Guttmacher & Collins, 2002). Conceivably, one might envision an approach to personalized medicine that includes sequencing an individual's genome at birth, thus generating a personal genome database, which can then be interrogated repeatedly throughout the patient's lifetime to predict and prevent diseases for which the person is at high risk, as well as optimize therapeutic interventions as genome guided therapies evolve.

A. The Importance of the Pedigree

The pedigree is one of the most essential tools in genetics. It depicts which family members are affected with a genetic condition, which family members are unaffected, and the relationships among the family members. A standardized format for pedigree notation is widely accepted (Bennett et al., 1995). The simplest human genetic diseases are those in which the genotype at a single locus is necessary and sufficient to result in the disease. This category of diseases is known as Mendelian diseases, because they follow the principles discovered by the Augustinian monk Gregor Mendel (1822–1884) by crossbreeding garden peas in the monastery gardens. Mendel's two fundamental principles are the *principle of segregation*, which states that only one of a pair of genes is transmitted to the offspring; and the *principle of independent assortment*, which states that genes at different chromosomal loci are transmitted independently of each other. Mendel also defined dominance and recessiveness, recognizing that the effects of one allele may mask those of the second allele. Many neurological diseases follow a Mendelian inheritance pattern (see Table 1.2; Pulst, 2003). They may be recognized because of their characteristic pedigree patterns (see Figure 1.1).

B. Mendelian Patterns of Inheritance

1. Autosomal Dominant Inheritance

An autosomal dominant (AD) trait is observable in the heterozygote state. In a classical AD trait, males and females are equally likely to be affected, and equally likely to transmit the trait to their offspring, there is no skipping of generations (i.e., at least one person in each generation is affected), vertical transmission from parent to child occurs, unaffected persons do not transmit the trait, and an affected individual passes on the trait to half of his or her offspring. Examples of neurological diseases inherited as an autosomal trait include Huntington's disease, myotonic dystrophy 1 and 2, neurofibromatosis 1 and 2, and many forms of spinocerebellar ataxia.

Table 1.2 Selected Neurological Disease Genesa

Disease	Inheritance	Locus	Gene	Gene Product	Year Identified
Peripheral Neuropathies					
Charcot-Marie-Tooth (CMT) 1A	AD	17p11.2	PMP22	Peripheral myelin protein 22	1991
X-Linked Charcot-Marie-Tooth	XLD	Xq13.1	GJB1	Connexin 32	1993
CMT 4A	AR	19q13.1	PRX	Periaxin	2001
Muscular Dystrophies					
Duchenne muscular dystrophy	XLR	Xp21.2	DMD	Dystrophin	1987
Myotonic dystrophy 1	AD	19q13.2	DMPK	Dystrophia myotonica protein kinase	1992
Myotonic dystrophy 2	AD	3q13	ZNF9	Zinc finger protein 9	2001
Neurocutaneous Diseases					
Tuberous sclerosis	AD	9q34	TSC1	Hamartin	1997
Tuberous sclerosis	AD	16p13.3	TSC2	Tuberin	1993
Neurofibromatosis 1	AD	17q11.2	NF1	Neurofibromin	1990
Neurofibromatosis 2	AD	22q12.2	NF2	Neurofibromin 2 or Merlin	1993
Mental Retardation Syndromes					
Fragile X syndrome	XLR	Xq27.3	FMR1	Frataxin	1991
Rett syndrome	XLD	Xq28	MECP2	Methyl CpG-binding protein 2	1999
Cortical Development					
Schizencephaly	AD	10q26	EMX2	Homeobox containing "Empty Spiracles" homolog	1996
X-linked lissencephaly and double cortex syndrome	XL	Xq22.3	DCX	Doublecortin	1998
Isolated lissencephaly sequence	AD	17p13.3	LIS1	Platelet activating factor acetylhydrolase, isoform 1B, alpha subunit	1993
Stroke					
CADASIL	AD	19p13.2	NOTCH3	Notch3	1996
Leukodystrophy					
Adrenoleukodystrophy	XLR	Xq28	ABCD1	ATP-binding cassette, subfamily D	1993
Leukoencephalopathy with vanishing white matter or ovarioleukodystrophy	AR	2p23	EIF2B4	Subunits of eukaryotic translation initiation factor EIF2B	2002
		14q24	EIF2B2		2002
		12	EIF2B1		2002
Neurodegenerative diseases					
Spinocerebellar ataxia 1	AD	6p23	ATXN1	Ataxin 1	1994
Spinocerebellar ataxia 2	AD	12q24	ATXN2	Ataxin 2	1996
Huntington disease	AD	4p16.3	Huntington	Huntington	1993
Parkinson disease	AD	4q21	SNCA	Alpha synuclein	1997
Parkinson disease	AR	6q25	PARK2	Parkin	1998
Parkinson disease	AR	1p36	DJ1	DJ1	2003
Parkinson disease	AD	12q12	LRRK2	Dardarin	2004
Alzheimer disease	AD	21q21	APP	Amyloid precursor protein	1991
Alzheimer disease	AD	14q24.3	PS1	Presenilin 1	1995
Alzheimer disease	AD	1q31-q42	PS2	Presenilin 2	1995
Epilepsies					
Generalized epilepsy febrile seizures +	AD	2q24	SCNA1	Voltage-gated sodium channel	2000
Generalized epilepsy febrile seizures +	AD	2q24	SCN2A1	Voltage-gated sodium channel	2004
Benign familial neonatal convulsions	AD	20q13.3	KCNQ2	Voltage-gated potassium channel	1998
Juvenile myoclonic epilepsy	AD	5q34-q35	GABRA1	Gaba A receptor subunit	2002
Unverricht-Lundborg	AR	21q22.3	EPM1	Cystatin B	1996
Lafora disease	AR	6q24	EPM2A	Laforin	1998
Channelopathies					
Hyperkalemic periodic paralysis	AD	17q23	SCN4A	Voltage-gated sodium channel	1991
Hemiplegic migraine 1	AD	19p13	CACNA1A	Voltage-gated calcium channel	1996
Myotonia congenita	AD/AR	7q35	CLCN1	Voltage gated chloride channel	1992
Erythromelalgia	AD	2q24	SCN9A	Voltage-gated sodium channel	2004

aThis table is not comprehensive, and illustrates only a few of the wide range of neurological conditions for which the genetic basis is known.