

REVIEW

De novo mutations in neurological and psychiatric disorders: effects, diagnosis and prevention

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Abstract

Neurological and psychiatric disorders account for a considerable proportion of the global disease burden. Although there is a high heritability and a significant genetic component in these disorders, the genetic cause of most cases has yet to be identified. Advances in DNA sequencing allowing the analysis of the whole human genome in a single experiment have led to an acceleration of the discovery of the genetic factors associated with human disease. Recent studies using these platforms have highlighted the important role of *de novo* mutations in neurological and psychiatric disorders. These findings have opened new avenues into the understanding of genetic disease mechanisms. These discoveries, combined with the increasing ease with which we can sequence the human genome, have important implications for diagnosis, prevention and treatment. Here, we present an overview of the recent discovery of *de novo* mutations using key examples of neurological and psychiatric disorders. We also discuss the impact of technological developments on diagnosis and prevention.

The impact of *de novo* mutations in neurological and psychiatric disorders

Neurological and psychiatric disorders account for 13% of the global disease burden [1], directly affecting more than 450 million people worldwide. The prevalence of these disorders is likely to continue to increase as a result of the increasing life expectancy of the population. Improved diagnosis and treatment would translate into a significant improvement in the quality of life of a large

proportion of the population, as well as the reduction of disease-associated costs, yielding significant benefits at clinical and societal levels. For example, almost half of patients with schizophrenia are currently not receiving appropriate healthcare, in part because early symptoms are often confused with those observed in other psychiatric disorders (for example, psychotic depression or bipolar disorder [2]). Other disorders such as Rett syndrome (RTT) and neurofibromatosis type II (NF2) require a multidisciplinary approach in specialized treatment centers, thus leading to high healthcare costs that could be reduced if better treatments were available.

It has long been known that neurological and psychiatric disorders run in families, suggesting heritability with a major genetic component to the disease. For some neurological disorders, such as NF2 or RTT, the genetic cause has been identified. However, for the great majority of neurological and psychiatric disorders, such as schizophrenia, autism, bipolar disorder and restless legs syndrome, the genetic causes remain mostly unknown. Recent developments in DNA sequencing technologies have opened new windows into our understanding of the genetic mechanisms underlying these disorders. Using these high-throughput massively parallel DNA sequencing platforms (also called 'next generation') it is now possible in a single experiment to search for mutations in all genes of the human genome. A major discovery arising from the use of these platforms is the importance of *de novo* mutations (that is, acquired mutations in the offspring) in psychiatric disorders such as intellectual disability (ID) [3-5], autism [6-10] and schizophrenia [11-16]. Indeed, in many recent genome-scale studies, analyzing the genomes of affected individuals and comparing these with their parents' genomes showed that rare *de novo* coding and non-coding variations are significantly associated with risk for autism and schizophrenia [6,8,10,12,17]. The large number of new cases of these disorders has been hypothesized to partly result from *de novo* mutations that might compensate for allele loss due to severely reduced reproductive fitness, thereby maintaining high frequencies of these diseases [18].

The role of *de novo* mutations in human diseases has been well recognized, particularly in the area of cancer

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genetics and in dominant Mendelian disorders such as Kabuki and Schinzel–Giedion syndromes [19,20], both of which are characterized by severe ID and congenital facial abnormalities, and have recently been found to be caused by *de novo* mutations in *MLL2* and *SETBP1* genes, respectively. Surprisingly, *de novo* mutations are rather common (in the order of 100 new mutations per child), with only a few (in the order of one per child) in coding regions [13,21], and have been found to be potentially disease-associated mutations (Table 1). *De novo* mutations outside coding regions, for example in promoter, intron or intergenic regions, can also be disease-associated. However, the challenge is to identify which of these mutations are pathogenic. Veltman and Brunner effectively summarized how interpretation of the pathogenicity of a *de novo* mutation should be established [18]. The following four major lines of evidence need to be taken into consideration when evaluating the pathogenicity of an observed *de novo* mutation: the *de novo* mutation rate, the gene function, the mutation impact and the clinical correlations (reviewed by Veltman and Brunner [18]). The main questions now are: How many genes will be involved in these disorders? What specific gene pathways are involved? What are the implications of *de novo* mutations for genetic counseling? These questions need to be investigated to improve diagnosis and to develop treatments.

In this review, we present an overview of the role of *de novo* mutations in neurological or psychiatric disorders. We use RTT, NF2 and schizophrenia to illustrate the different scenarios involving *de novo* mutations and how they can act and lead to a disorder. We also discuss how recent technological developments might influence how we make diagnoses, and we conclude by examining how prevention might be implemented in neurological and psychiatric disorders known to be linked to *de novo* mutations.

Effects

Neurological and psychiatric disorders

The brain governs the entire human body by controlling thoughts, memory, speech, movements and autonomic functions. Any deficiency at the level of one of these functions and/or structures, including neurons, cerebral blood vessels or meninges, is likely to lead to a 'brain disorder'. A brain disorder refers to a large category of illnesses and includes diseases characterized by various clinical symptoms, severities and ages of onset. This group includes neurological and psychiatric disorders (for example, NF2, schizophrenia, RTT and many others), which are the focus of this article. Neurological disorders affect the nervous system and psychiatric disorders are largely defined by patterns of abnormal thoughts and emotions, and maladaptive behavior and social interaction.

More than 600 such disorders have been defined, including 300 psychiatric disorders indexed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [22], the standard diagnostic tool for psychiatric disorders. Both groups of disorders are currently diagnosed by a physician based on clinical symptoms. Unfortunately, for the great majority of these disorders, no biological test is available. In addition, most of these disorders are complex, resulting from the interplay of genetic and environmental factors.

Genetic perspectives

Based on evidence from twin studies, the heritability of some disorders has been observed to be high. This is the case for autism and schizophrenia, with heritabilities in the order of 90% [23] and 80% [24], respectively. However, these diseases also frequently occur as isolated cases, with only one affected child born to unaffected parents with no family history of the disease. One possible explanation is the occurrence of '*de novo*' mutations, where mutations occur during spermatogenesis or oogenesis (germline mutations), and are therefore present in the patient but undetectable in the unaffected parent. This genetic mechanism has recently been the focus of considerable attention to explain part of the genetic basis of neurodevelopmental disorders.

According to the Allen Human Brain Atlas database [25], more than 82% of all human genes are expressed in the brain. Given that the human genome is estimated to contain 22,333 genes [26], this suggests that more than 17,800 genes are expressed in the human brain. Mutations affecting almost any of these genes, combined with environmental factors, may contribute to brain disorders. Recent studies have identified a number of causal mutations in brain-expressed genes and have revealed the considerable role that genetics plays in neurological and psychiatric disorders. These studies have highlighted the involvement of rare (<1% frequency) point mutations and copy-number variations (CNVs; that is, genomic deletions or duplications of >1 kb to several Mb in size) that can occur in gene-free regions, or which may affect one gene or include a contiguous set of genes in the genetic etiology of autism, schizophrenia, ID, attention deficit disorder and other disorders [3,6–11,13,15,16,27–29]. Using studies of trios (that is, affected child and parents) with sporadic schizophrenia or autism (that is, with no history of psychiatric disorders in the parents or the extended family), we and others have observed a significant excess of potentially deleterious *de novo* mutations in the cases. Recently, the studies of Sanders *et al.*, Neale *et al.*, O'Roak *et al.* and Iossifov *et al.* have confirmed the contribution of *de novo* mutations to autism [6,8–10]. Each study identified a list of *de novo* mutations present in probands, but only a handful of genes were identified

Table 1. Examples from the literature of human brain disorders and genes implicated in diseases associated with *de novo* mutations

Disorders	OMIM	Implicated gene(s)	References
Alexander disease	#203450	<i>GFAP</i>	Brenner <i>et al.</i> , 2001 [73]
Amyotrophic lateral sclerosis	#105400	<i>FUS, TDP-43, SOD1</i>	DeJesus-Hernandez <i>et al.</i> , 2010 [74]
Ataxia	#208920	<i>CACNA1A, TBP</i>	Koide <i>et al.</i> , 1999 [75]
Autism spectrum disorders	#209850	<i>NLGN3, NLGN4, NRXN1, SHANK3, etc.</i>	Jamain <i>et al.</i> , 2003 [67]; Durand <i>et al.</i> , 2007[39]
CADASIL	#125310	<i>NOTCH3</i>	Joutel <i>et al.</i> , 2000 [76]
Cerebral cavernous malformations	#116860	<i>KRIT1, CCM2, CMM3, PDCD10</i>	Lucas <i>et al.</i> , 2001 [77]; Bergametti <i>et al.</i> , 2005 [78]
Charcot–Marie–Tooth disease	#606482	>10 genes	Boerkoel <i>et al.</i> , 2002 [79]
Dejerine–Sottas	#145900	<i>PMP22</i>	Valentijn <i>et al.</i> , 1995 [80]
Dravet syndrome	#607208	<i>SCN1A</i>	Claes <i>et al.</i> , 2001 [81]
Early-onset dementia	#600274	<i>PRNP, APP</i>	Cannella <i>et al.</i> , 2007 [82]; McNaughton <i>et al.</i> , 2012 [83]
Focal epilepsy	#300088	<i>SCN1A</i>	Okumura <i>et al.</i> , 2007 [84]
Hemiplegic migraine	#141500	<i>ATPA2, CACNA1A</i>	Riant <i>et al.</i> , 2010 [85]
Intellectual disability	#612621	<i>SYNGAP1</i>	Hamdan <i>et al.</i> , 2009 [4]
Neurofibromatosis type II	#162200	<i>NF1</i>	Viskochil <i>et al.</i> , 1990 [86]
Neurofibromatosis type II	#101000	<i>NF2</i>	Rouleau <i>et al.</i> , 1993 [53]
Rapid-onset dystonia Parkinsonism	#128235	<i>ATP1A3</i>	Post <i>et al.</i> , 2009 [87]
Rett syndrome	#312750	<i>MECP2, CDKL5 and netrin G1</i>	Amir <i>et al.</i> , 1999 [44]; Weaving <i>et al.</i> , 2004 [88]; Borg <i>et al.</i> , 2005 [89]
Schizophrenia	#181500	<i>SHANK3, NRXNs</i>	Gauthier <i>et al.</i> , 2010 [14]; Rujescu <i>et al.</i> , 2009 [90]

with multiple *de novo* hits (that is, *CHD8*, *SCN2A*, *KATNAL2* and *NTNG1* genes). Protein-interaction network and pathway-based analyses from these studies showed significant connectivity and a common biological pathway among genes harboring *de novo* mutations in cases with autism. Protein networks implicated in chromatin remodeling, ubiquitination and neuronal development have been identified as potential targets for autism susceptibility genes. Finally, these studies suggest that 1,000 or more genes may be implicated as those in which highly penetrant autism-contributing mutations can occur [6,8-10].

De novo mutations: roles, causes and implications

Technological advances in DNA sequencing have revolutionized the study of genetic variation in the human genome and have allowed the identification of many types of mutations, including single-base pair substitutions, insertions/deletions, CNVs, inversions and repeat expansions, as well as both somatic and germline mutations. All these types of mutations have been shown to play a role in human disease. Single nucleotide mutations appear to be largely of paternal origin, whereas deletions may be largely of maternal origin. This could be explained by the differences between male and female gametogenesis. For example, in a study of neurofibromatosis, 16 of 21 mutations consisted of deletions of maternal origin and 9 of 11 point mutations were of paternal origin [30].

The various mutation types can either be transmitted from a parent to a child or acquired spontaneously. The mechanism directing the latter has attracted attention in recent years due to the importance of this type of mutation in diseases such as schizophrenia and autism. The rate of *de novo* mutations appears to be dominated by the age of the father [31]. The rate increases with increasing paternal age, possibly due to the consequences of reduced efficiency of DNA replication or repair mechanisms, which are expected to deteriorate with age [31,32]. Therefore the risk for a disease should increase with increasing paternal age. This has been found to be the case in many disorders, including Crouzon syndrome [33], multiple endocrine neoplasia type II [34] and neurofibromatosis type I [35]. More recently, O’Roak *et al.* observed a marked paternal bias of 51 *de novo* mutations identified through an exome sequencing study of 189 parent–child trios with cases of sporadic autism. Their findings are similar to those observed from recent reports on *de novo* CNVs in ID [36]. This correlation could be explained by the significantly higher number of mitotic cell divisions in germ cells or spermatocytes prior to meiosis over the lifetime of men, compared with that which occurs in oogenesis in women. Based on the established number of cell divisions occurring in oogenesis (from birth to menopause) compared with spermatogenesis (from puberty to the end of life), James F. Crow estimated that by age 30 years the average number of

chromosome replications from the zygote to sperm formation is 16.5-fold higher than from zygote to ovum formation [37].

Mosaicism and recurrent risk of disease

Genetic mosaicism is caused by the occurrence of *de novo* mitotic mutations very early in the development of the embryo and is defined as the presence of multiple cell clones with a distinct genotype in the same individual. Both somatic and germline mosaicism exist, but germline mosaicism may contribute to the transmission of what might appear to be a *de novo* mutation to the offspring. Germline mosaicism involving the *SHANK3* gene has been described by our group in a schizophrenia kindred [14]. We detected a nonsense *de novo* (R1117X) mutation in a proband and his two affected brothers that appeared to be paternally inherited based on haplotype analysis, and is likely to be due to germline mosaicism. This phenomenon has been documented in more than 60 genetic diseases, including many brain disorders [38]. For example, Durand *et al.* and Moessner *et al.* reported families with two affected siblings with apparently healthy parents, carrying the same *de novo* frame-shift *SHANK3* mutation and the same *de novo* 4.4 Mb deletion, respectively [39,40]. In both cases, the mutation was absent in blood DNA of the unaffected parents. In these cases where unaffected parents have multiple affected children carrying the same *de novo* mutation, germline mosaicism is inferred. Parental allelic origin can be determined using molecular cloning and informative markers in one of the parents that are linked to the *de novo* events. One would normally expect the risk of the same *de novo* mutation occurring in a subsequent sibling to be equivalent to zero or to be smaller than the *de novo* mutation rate baseline estimate of 1.1×10^{-8} to 1.2×10^{-8} [13,31,41,42], which is the frequency of new single nucleotide variants per generation in humans. However, this is not the case when germline mosaicism exists. In a literature review on germline mosaicism, Helderman-van den Enden *et al.* found that among seven diseases with known recurrence risk for *de novo* mutation, the risk of recurrence due to germline mosaicism varied from 0.02% in achondroplasia to 11% in RTT, 13% in hemophilia A and 20% in Duchenne muscular dystrophy [38]. The reason why recurrence risk varies significantly from one disease to another remains obscure. Unfortunately, for most diseases the recurrence risk of *de novo* mutations originating from germline mosaicism has not been studied. This information will be important for genetic counseling, where a reliable estimate of recurrent risk is needed.

Spontaneous mutations arising in somatic cells (during mitosis, after fertilization) may also play a role in neurodevelopmental diseases. Such mutations would not normally be passed to the offspring, except if they

occurred in cells that later formed the germline. Thus, throughout life, in addition to inherited mutations, an individual will accumulate genetic mutations in many different cells. Somatic mutations result from factors that include defective DNA repair or DNA replication, and agents that damage DNA, such as exposure to radiation, cigarette smoke or certain drugs. Next-generation sequencing technologies are now allowing researchers to better study the prevalence of somatic mutations and their involvement in disease [43].

***De novo* mutations in neurological and psychiatric disorders: three possible scenarios**

As mentioned earlier, *de novo* mutations can be of various types and can originate from paternal or maternal chromosomes. In addition, these mutations can act in dominant or recessive manners, as well as in combination with somatic *de novo* mutations. This section aims to illustrate these different scenarios based on RTT, NF2 and schizophrenia as examples of diseases associated with *de novo* mutations (Figure 1).

RTT: one gene

RTT is one of the most common causes of severe ID in girls, with an incidence of 1:10,000 live female births. Most cases of RTT are sporadic, with no familial history of the disease. We now know that the majority of patients with RTT have a *de novo* mutation in the X-linked gene encoding methyl CpG binding protein 2 (*MECP2*) [44]. Most of these *de novo* mutations arise on the paternal X chromosome [45,46], increasing in frequency with paternal age, which is consistent with the hypothesis that point mutations occur more frequently during spermatogenesis than oogenesis. Very few families have been described with multiple affected individuals, but these have typically involved siblings (for example [47,48]) where transmission occurs from asymptomatic mothers with skewed X-chromosome inactivation [48] or by parental gonadal mosaicism [49]. Thus, the example of RTT clearly illustrates that, for neurological or psychiatric disorders, new mutations can act in a dominant manner to cause disease.

Schizophrenia: multiple genes

Schizophrenia is a chronic and severe mental illness characterized by profound disruption in cognition, behavior and emotion. Although there may be some variations, the prevalence of schizophrenia is reported to be 1% in the population over the age of 18 years [50], a frequency that is maintained across different ethnic groups, cultures and geographic regions [51]. Schizophrenia is a complex brain disorder suspected to result from both genetic and environmental influences. Recent advances in sequencing technologies have greatly helped

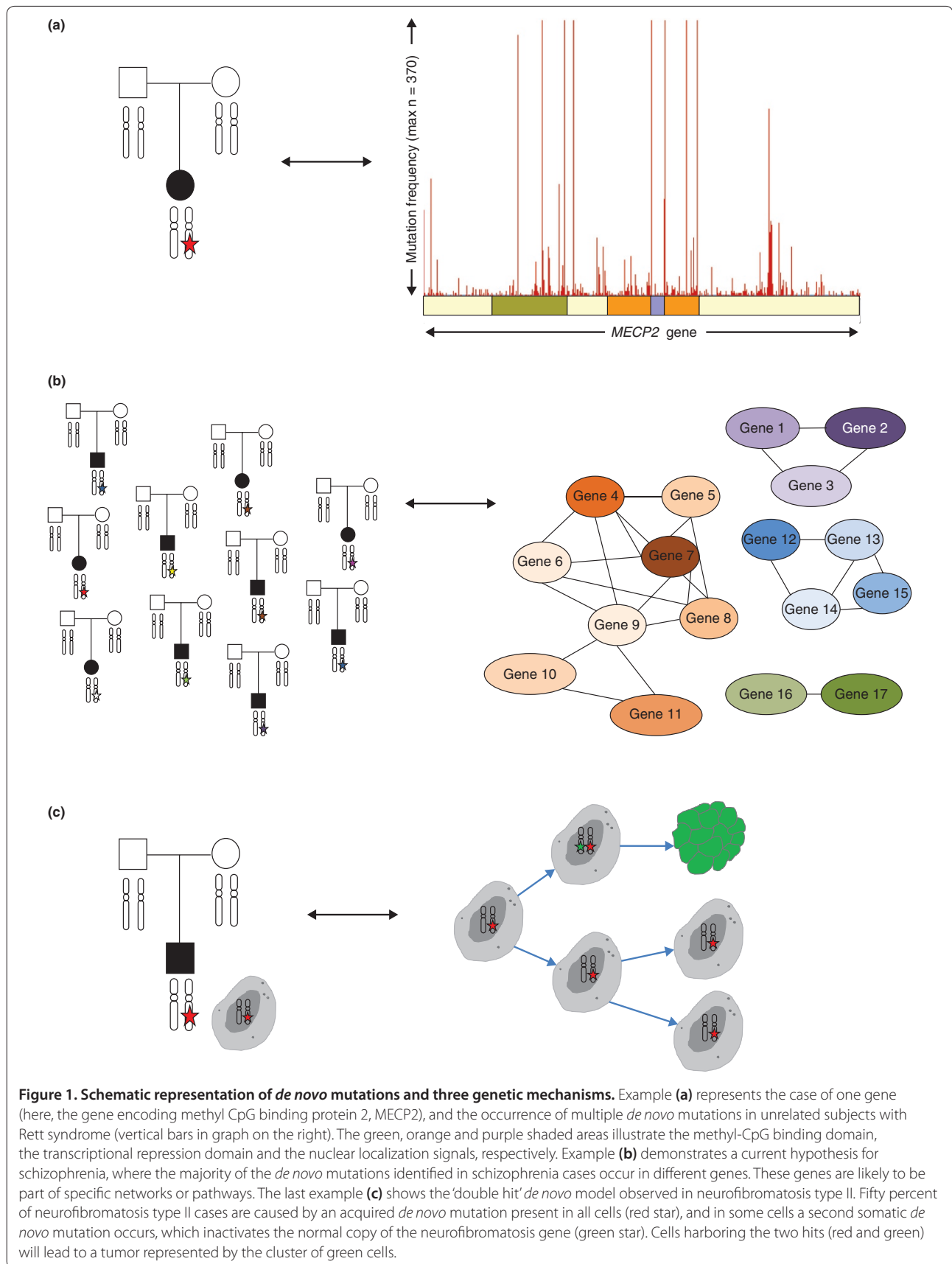


Figure 1. Schematic representation of *de novo* mutations and three genetic mechanisms. Example (a) represents the case of one gene (here, the gene encoding methyl CpG binding protein 2, MECP2), and the occurrence of multiple *de novo* mutations in unrelated subjects with Rett syndrome (vertical bars in graph on the right). The green, orange and purple shaded areas illustrate the methyl-CpG binding domain, the transcriptional repression domain and the nuclear localization signals, respectively. Example (b) demonstrates a current hypothesis for schizophrenia, where the majority of the *de novo* mutations identified in schizophrenia cases occur in different genes. These genes are likely to be part of specific networks or pathways. The last example (c) shows the 'double hit' *de novo* model observed in neurofibromatosis type II. Fifty percent of neurofibromatosis type II cases are caused by an acquired *de novo* mutation present in all cells (red star), and in some cells a second somatic *de novo* mutation occurs, which inactivates the normal copy of the neurofibromatosis gene (green star). Cells harboring the two hits (red and green) will lead to a tumor represented by the cluster of green cells.

to strengthen the importance of the role of rare *de novo* variants in schizophrenia. As an example, to investigate the possibility that *de novo* protein-altering mutations contribute to the genetic component of schizophrenia, Xu *et al.* and Girard *et al.* sequenced the exomes of 53 and 14 sporadic cases and their parents, respectively [11,12]. The studies' results were concordant. Although not all *de novo* mutations are necessarily pathogenic, some of the ones identified in these studies are likely to be responsible for the schizophrenia phenotype based on several lines of evidence, such as the observed large excess of non-synonymous *de novo* point mutations compared with neutral ones, and the observed enrichment of predicted deleterious non-synonymous variants (relative enrichment 12.1; chi-squared test, $P < 0.0001$ [12]). It is interesting to note that the majority of the *de novo* mutations associated with susceptibility to schizophrenia to date occur in many different genes. Thus, the sporadic form of schizophrenia seems to be associated with multiple genes, suggesting a high level of non-allelic genetic heterogeneity. This might explain why the global incidence of schizophrenia is relatively uniform, and the disease is maintained at a similar frequency despite extremely variable environments and poor reproductive fitness [52].

NF2: two-hit model

NF2 is a rare monogenic disorder characterized by bilateral vestibular schwannomas as well as other spinal and peripheral tumors. The tumor suppressor gene *NF2*, which maps to chromosome 22q11.2, was isolated in 1993 by two independent groups [53,54]. Nearly 50% of cases represent new mutations in individuals with no family history of the disease. Individuals with NF2 have one copy of the gene inactivated in all their cells; for tumor development specific cells need to have a somatic *de novo* mutation(s), which inactivates the normal copy of the *NF2* gene. In the case of sporadic schwannomas, specific cells need to have somatic mutations inactivating both copies of the *NF2* gene. Hence, the disease is inherited in a dominant manner, but acts in a recessive manner at the cellular level. Knudson proposed this 'two-hit' model early in 1971 from his observations in retinoblastoma [55].

As discussed earlier, *de novo* mutations can lead to a monogenic dominant (for example, RTT) or monogenic recessive (for example, NF2) Mendelian form of disease, and even to a form of disease in which a large number of different genes is implicated (schizophrenia). The latter mechanism is expected to be prominent in other psychiatric disorders such as autism, ID and bipolar disorder.

Diagnosis

Next-generation DNA sequencing technologies are now commonly used in research, and an increasing number of

institutions and clinical laboratories are offering molecular genetic analysis based on this method. These tests may be used to identify disease-predisposing mutations or to identify genetic variants that might in part predict development of diseases as well as indicate those individuals who are most likely to respond to specific medications or interventions.

The role and impact of technological developments

Whole genome and exome sequencing are powerful research tools to identify predisposing genes underlying a variety of disorders where other conventional methods have limited success. The main reason for the previous lack of success is allelic and non-allelic genetic heterogeneity, with dozens to perhaps hundreds of genes predisposing to each diagnostic entity, and each gene having many allelic variants. This is exemplified by recent studies of autism using parent-child trios [6,8-10]. Mutations in genes predisposing to severe diseases where there is a strong negative selection against the phenotype, such as lethality in embryonic stages or reduced reproductive fitness, will not be transmitted to multiple family members, and therefore will not be detected by gene linkage mapping.

The successful use of whole genome and exome sequencing for diagnosis has been confirmed in numerous studies. Whether exome sequencing will eventually be replaced by whole genome sequencing is still unknown. Although most mutations are found in coding regions, it is thought that both exome and whole genome sequencing will coexist [56]. Interestingly, based on sequencing the same sample, Clark *et al.* demonstrated that exome and whole genome sequencing are complementary. Exome sequencing can detect variants not detected by whole genome sequencing and *vice versa* [57]. However, an important challenge in using whole genome sequencing will be the interpretation of the data. We expect that whole genome sequencing will allow the identification of genetic variants that will determine an individual's risk of developing diseases, including neurological or psychiatric disorders. In fact, the continuing reduction in sequencing costs may lead to replacement of most of the other currently used approaches.

Prenatal diagnosis

The rapid development of sequencing is now having a positive impact on prenatal diagnosis. Since the discovery of cell-free fetal nucleic acids circulating in the blood of pregnant women [58], combined with the development of next-generation DNA sequencing technologies, it is now possible to perform early, non-invasive prenatal genetic testing [59]. The major advantage is to provide genetic information about the fetus avoiding a health risk due to the current invasive approaches, such as

amniocentesis. In addition to causing stress for pregnant women, performing this invasive procedure and the analyses are costly, and entail a significant fetal loss rate of 0.5 to 1% [60,61]. Thus, implementing sequencing technologies and approaches would have numerous clinical advantages. Clinical applications of these methods already include fetal sex determination and blood group typing [62]. Ongoing research is evaluating the use of this approach for non-invasive detection of trisomies [63]. Other uses being explored are the detection of single-gene disorders, a range of chromosomal abnormalities and inheritance of parental polymorphisms across the whole fetal genome. Two groups have recently demonstrated that it is now technically feasible to non-invasively sequence the entire fetal genome [64,65]. While technical, analytical and ethical challenges remain, it is likely that this approach will be integrated into clinical practice in the near future.

Clinical versus genomic diagnosis

Most disorders are clinically defined and diagnostic tools aim at facilitating the 'clinical diagnosis'. A 'genomic diagnosis' is based on the analysis of the genetic information contained in the patient's DNA to determine whether the patient carries a genetic defect associated with a disease. Genomic approaches offer the opportunity to identify risk factors prior to or very early after disease onset, allowing earlier and more efficacious interventions focused on prevention rather than treatment. Establishing an accurate diagnosis is the foundation on which medicine is based. Upon learning that their child has a disorder, most parents wish to understand the cause of the condition and are concerned about the risk of recurrence in other offspring. Diagnostic techniques based on molecular genetics provide concrete answers to these questions. Establishing an accurate diagnosis based on genetic analysis presents significant advantages, reducing the usual battery of tests required to pinpoint the cause of a disorder. For example, children with ID typically undergo a series of investigations, brain imaging, metabolic studies, cytogenetic and molecular genetics testing, to make an etiological diagnosis. A high performing genomic test introduced at the beginning of this process may obviate the need for costly, time-consuming and stressful assessments in a large proportion of cases.

While mutations in hundreds of susceptibility genes have already been described in brain disorders, genetic diagnostic assays are available for only a handful of genes. As an example, although non-syndromic ID could represent up to two-thirds of all ID cases, only about 50 causative genes have so far been identified [66], which explain less than 10% of sporadic cases, suggesting that the total number of non-syndromic ID genes is likely to be in the hundreds. It is now clear that the same clinical

diagnosis may not necessarily be given for the same genetic/genomic defect. This is indeed the case for the majority of brain disorders where *de novo* mutations occur in different genes. By contrast, a single gene may lead to different diagnoses. For example, one *de novo* mutation in the X-linked *NLGN3* gene has been found to occur in an asymptomatic mother, who had two affected sons, one diagnosed with autism and the other with Asperger syndrome [67]. Although these disorders are clinically related, they correspond to distinct diagnoses in the current version of the DSM-IV [22]. As discussed by Boone *et al.* in a review of genomic medicine and neurological diseases [68], these observations bring us to ponder whether individuals may one day be given two distinct (or complementary) diagnoses: one clinical in nature, the other molecular. Guidelines for *de novo* mutation screening analysis, and more importantly, guidelines for mutation interpretation, will need to be elaborated as more and more laboratories will be offering exome or whole genome analysis for diagnostic purposes. Clearly, additional work is needed to establish lists of disease causative or predisposing genes, which should be part of diagnostic tests of genetically heterogeneous disorders. For example, determining mutation prevalence (for a range of specific mutations, as well as mutational frequency of any single gene), or the frequency at which any particular gene leads to any single phenotype, remains to be defined for most diseases. Both the clinical and genomic approaches aim to achieve diagnosis of a disease, and we consider that both approaches will remain complementary in the future.

Limitations and ethical issues

Although technically feasible, several challenges remain for using whole genome sequencing for diagnosis. Next-generation DNA sequencing technologies generate terabytes of data, and storing the amount of data that will be produced constitutes a challenge. In addition, processing these huge amounts of genetic information requires up-to-date computational power and time resources. Bioinformatic analysis still remains a bottleneck and negatively impacts on the 'turnover' time for giving results to patients. The major challenge remains the interpretation of data and linking the genetic variant to the disease.

Important ethical challenges also remain. For example, should incidental findings (that is, those found accidentally and not related to the disease being tested) identified by whole genome or exome sequencing be reported to the patient? There is currently no consensus regarding this issue in the field. In fact, whole human genome sequencing adds to the complexity of the genetic information that will be accessible, and raises great social concerns that still need to be resolved, such as possible forms of discrimination. Efforts have been made to

overcome this phenomenon since the Genetic Information Nondiscrimination Act was signed in the USA in 2008 to protect individuals from improper use of genetic information with regard to health insurance and employment [69]. Emerging discoveries of susceptibility genes and gene variants associated with major neurological or psychiatric disorders are likely to challenge the existing ethical guidelines. It is up to researchers, health professionals and experts in Ethical, Economic, Environmental, Legal, and Social aspects of genomics (GE3LS) to manage this growing scientific knowledge in a way that prioritizes protection of research participants and improves patient care.

Prevention and treatment

The identification of predisposing disease genes is essential to identify the disease-predisposing biological pathways. Early diagnosis opens avenues for interventions that could delay or prevent the development of neurological or psychiatric disorders. For example, an accurate molecular diagnosis in a patient with ID may lead to interventions that may result in improving the patient's intellectual abilities, making the difference between the need for permanent institutionalization and the ability to live and work with minimal intervention from caregivers.

If *de novo* mutations are indeed important contributing factors for neurological and psychiatric disorders, one issue that needs to be addressed is the identification of the factors contributing to higher mutation rates. Prevention may only be achieved once the 'mechanisms' underlying the cause of a disease are recognized. Parental age at the time of conception may be one factor contributing to a higher mutation rate. This has been recently confirmed by Kong *et al.*, who showed that the father's age is the dominant factor in determining the number of *de novo* mutations in a child [31]. By sequencing the entire genomes of 78 parent-child trios, including five families comprising three generations, Kong *et al.* found that the number of mutations increases with the father's age ($P = 3.6 \times 10^{-19}$) with an estimated linear effect of 2.01 mutations per year (standard error = 0.17), and an estimated doubling of paternal mutations every 16.5 years using an exponential model [31]. Other 'environmental' factors that may also be associated with *de novo* mutations need to be identified.

One of the future challenges will be to determine how genomic information may be used to predict the risk for developing medical conditions. Concomitantly, one must define the best ways and develop the best tools to manage this information and use it to improve quality of life and care of patients. This will be even more critical when translating this information into preventive measures aimed at achieving improved health. Given that new targeted treatments focusing on correcting (fully or

partially) genetic defects are likely to be available in the near future (for example, gene therapy for the treatment of frame-shifting mutations using antisense-induced exon skipping to restore the reading frame [70]), an accurate genetic diagnosis will inevitably define the appropriate treatment.

Conclusions and future directions

The availability of genomic information has increased significantly over the last decade through the development of high-throughput DNA sequencing technologies. The accessibility of these platforms has allowed an acceleration of the rate of discovery of DNA variations associated with disease. Therefore the number of genes being associated with brain disorders is increasing at an unprecedented rate. In other words, these techniques have completely changed gene identification approaches from single-gene screening to whole genome screening, and have become a powerful tool to identify disease genes, particularly where conventional methods have failed. The discovery of genetic variants underlying neurological and psychiatric disorders provides insights into disease mechanisms. A good example is the recent finding of the important role of *de novo* mutations in psychiatric disorders such as schizophrenia and autism. This discovery was only possible (or at least accelerated) with the ability to sequence the exome of an affected child and compare it with his/her parents. Although the role of *de novo* mutations in neurological and psychiatric disorders has been confirmed by several independent studies, many issues remain to be resolved. For example, what are the causes of *de novo* mutations? What is the percentage of cases affected by deleterious *de novo* mutations? Are certain genomic regions or certain genes more frequently prone to *de novo* mutations? All of these questions will be answered with the increasing amounts of exome or whole genome data available for analysis.

In turn, these discoveries will enable the development of improved diagnosis. However, the clinical use of diagnostic tests derived from these discoveries is lagging behind. One of the major challenges is to develop tools and methods that will help improve medical diagnosis. Knowing which genes are disrupted in a brain disorder such as autism will allow molecular diagnostic assays to be developed to better identify and define pathogenesis in affected individuals, and to do so at an earlier age.

Any new understanding of the pathological mechanisms of brain diseases is important for medicine and directly impacts the community. Early intervention in neurological or psychiatric disorders is likely to have a significant impact on outcome. Indeed, without effective intervention, most people with autism and other pervasive developmental disorders require lifelong specialized educational and care services, at a total cost that is

estimated at approximately US\$4 million per person [71]. The overall average savings from the implementation of an early intensive behavioral intervention program, such as a one-to-one behavioral-based treatment for children with autism, are estimated at US\$1 to 2 million per individual across their lifespan, without taking into account the human benefits [72]. Finally, establishing a definite genetic diagnosis of a disease, especially in children, can significantly reduce the levels of guilt and anxiety in parents and improve their compliance with educational intervention programs.

Abbreviations

CNV, copy-number variation; DSM, Diagnostic and Statistical Manual of Mental Disorders; ID, intellectual disability; NF2, neurofibromatosis type II; RTT, Rett syndrome.

Competing interests

The authors declare that they have no competing interests.

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