Thus, the history of research on BRCA1/2-associated risk demonstrates the greater power and precision of studies based on direct molecular analysis of relatives.

The limited correlation between genotype and phenotype even in single-gene disorders has focused interest on modifier genes or genetic background as an explanation for the highly variable phenotype even in single-gene disorders. A recent molecular analysis of relatives. The medical utility of any genetic test is critically dependent on the ability to predict the phenotype from the genotype (phenogenetics). The NYBCS results demonstrate that nongenetic effects of environmental origin must be understood if we are to reach the goal of personalized genetic medicine.

Clinical BRCA1/2 testing is generally performed in the setting of at least some family cancer history. In this respect, NYBCS risk estimates, which are nearly as high as those in high-risk families, are applicable to most current genetic counseling situations. Do these high risks also argue for wider testing for susceptibility mutations? Notably, 50% of mutation carriers in this study had no significant family history, and would have been identified before the onset of symptoms only if testing were performed in the general population. Identifying healthy BRCA1/2 carriers is meaningful because prophylactic removal of the ovaries is known to reduce both breast and ovarian cancer rates in these carriers (7, 8). However, studies specifically designed to address population testing are clearly needed. The NYBCS did not find evidence for familial clustering of risk-modifying factors. But there are grounds to suspect that in BRCA1/2 families identified through an affected individual (as in the NYBCS) all other cancer risk factors, and especially genetic modifiers, are more likely to be overrepresented and to inflate the level of risk attributed to BRCA1/2 mutations (9). In addition, as the NYBCS shows, cancer risk is also influenced by nongenetic factors, which would be highly variable in the general population. Genetic analysis of common diseases begins with selected families, is then applied to affected individuals, and can ultimately evolve into generally applicable testing (10). Results of the NYBCS suggest that the time has come for research studies to examine testing for BRCA1/2 mutations in the general population to determine if cancer risks are sufficient to justify general screening.

References

PLANT SCIENCES

How Legumes Select Their Sweet Talking Symbionts

Julie Cullimore and Jean Dénarié

Legumes such as soybean, pea, peanut, and alfalfa are able to fix nitrogen because of the bacterial symbionts (rhizobia) that inhabit nodules on their roots. The amount of ammonia produced by rhizobial fixation of nitrogen rivals that of the world’s entire fertilizer industry. Consequently, this symbiotic relationship between legumes and rhizobia is of great agronomic and ecological importance. Signals from rhizobial bacteria, called nod factors (lipochitooligosaccharides), are crucial for initiating the symbiotic response of legumes. This response leads to recognition of bacteria by root-hair cells, curling of root hairs, growth of infection threads, and finally the formation of root nodules (nodulation). The molecular events establishing this symbiosis are the subject of three reports, one by Limpens et al. (1) on page 630 of this issue and the other two by Stougaard’s group (2, 3) in a recent issue of Nature. These three papers identify genes of legumes that encode receptors involved in nod factor recognition, leading to the initiation of infection by rhizobia. These receptors belong to a family of plant transmembrane receptor–like serine/threonine kinases (RLKs) whose extracellular regions contain LysM domains (LysM-RLKs).

Plants often establish symbiotic relationships with bacteria and fungi in order to acquire the nutrients they need to support growth and development. The plant symbiotic relationships most studied are those involving rhizobial bacteria and mycorrhizal fungi (4, 5). Although these symbiotic relationships may not, at first sight, appear to have much in common, both bacterial and fungal symbiotic partners are able to trigger the plant host genetic program that permits localized infection and controlled growth (4, 5).

Rhizobial access to the root cortex where nodule formation begins depends on initial recognition of the bacteria by epidermal root-hair cells, followed by root-hair curling and the formation of infection threads (see the figure). Nod factors released by rhizobia are required to establish the earliest steps of the legume-bacterial symbiotic relationship. These molecules are tetramers and pentamers of the carbohydrate chitin, which are attached to a fatty acid chain (5). Species-specific chemical substitutions in the sugars, combined with structural differences in the
Discriminating root hairs. (A) Symbiotic rhizobial bacteria secrete Nod factors that are perceived by two transmembrane LysM-RLKs, NFR1 and NFR5. The activated (putative) NFR1/NFR5 heterodimer initiates rapid calcium influx and swelling of root-hair tips, which are early events in the plant symbiotic response that might be specific for bacterial symbionts. Activation of NFR1/NFR5 is also required to activate the putative receptor complex, NORK/DM1, which results in plant symbiotic responses to both bacterial and fungal symbionts. The NORK/DM1 complex may also be involved in direct recognition of rhizobial and mycorrhizal signals. (B) Rhizobial bacteria entrapped in a curling root hair. In order for rhizobia to enter root hairs and to initiate formation of infection threads and nodulation, the Nod factors they release must be recognized by highly specific plant receptors. The LysM-RLKs LYK3 and LYK4 of *M. truncatula* are involved in Nod factor recognition. (C) NFR5 has three LysM domains and its kinase domain does not contain an activation loop. NFR1, LYK3, and LYK4 have two LysM domains, and their kinase domains contain an activation loop. SP, signal peptide; TM, transmembrane domain; AL, activation loop in the kinase domain. [Data from (1–3, 6, 7)]

Perspectives

Characterization of Nod factor receptor genes (1–3). Limpens, Bisseling, and colleagues identify a cluster of seven genes (*LYK1*–7) in *M. truncatula* that are syntenic with the *SYM2A* region of pea (1). Using RNA interference (RNAi), Limpens et al. demonstrate that the *LYK3* and *LYK4* genes are required for Nod factor–induced infection of root-hair cells by rhizobia. In their complementary pair of studies, Stougaard and co-workers show that the *NFR1* and *NFR5* genes encode receptors required for Nod factor recognition in *L. japonicus* (2, 3).

The *NFR5* gene of *L. japonicus* contains a single exon encoding an RLK with an extracellular region containing three LysM domains and an intracellular kinase domain lacking the typical activation loop (3, 9). This gene appears to be orthologous to pea *SYM10* and *M. truncatula* NFP genes (3, 7, 8). The *NFR1* gene of *L. japonicus* has 12 exons and encodes an RLK containing two LysM domains in the extracellular part and a kinase domain with an activation loop (2, 9); this receptor shares only about 30% identity with *NFR5* (2). The *M. truncatula* *LYK3* and *LYK4* genes have a similar 12-exon structure encoding proteins with two LysM domains and a kinase domain very similar to that of *NFR1* (1) (see the figure).

Five genes encoding putative LysM-RLKs have been identified in the model plant *Arabidopsis thaliana* (10), and related genes have been found in rice and other plants. This suggests that the LysM-RLKs of symbiotic legumes have evolved from a preexisting class of plant LysM-RLKs.

Do the newly identified genes actually encode Nod factor receptors? LysM domains were originally identified as 40- to 50-residue sequences present in lysins and other bacterial enzymes that degrade bacterial cell walls. These domains are commonly found in bacteria, are absent in archaea, and show a patchy distribution in eukaryotes. Most LysM proteins contain one to three LysM domains (11). The LysM domains of the bacterial autolysin produced by *Lactococcus lactis* interact with the glycan part of peptidoglycans (12). In eukaryotes, LysM domains are found in some chitinases and in a variety of proteins whose functions are, for the most part, unknown. The phenotype of the legume mutants described in the new studies (1–3), coupled with our current knowledge of LysM domains, strongly suggests that the symbiotically active LysM-RLKs—*NFR1*, *NFR5*, and *LYK3*—are receptors for rhizobial Nod factors. It is tempting to speculate that nonsymbiotic LysM-RLKs may be important for the “perception” of oligosaccharide ligands involved in plant defense and development.

In *L. japonicus*, both *NFR1* and *NFR5* are required for early Nod factor responses.
which suggests that they may operate as a heterodimer (2). In pea and *M. truncatula*, a complete defect in Nod factor responses has only been observed with mutations in genes orthologous to NFR5; the lack of null mutations in a second locus (orthologous to NFR1) might be due to functional redundancy. In *M. truncatula* both LYK3 and LYK4 are required for Nod factor–dependent infection of root-hair cells (1). Thus, the formation of heterodimers could be a general feature of Nod factor receptors in legumes.

In pea, vetch, *Medicago sativa*, and *M. truncatula*, the structural requirements for Nod factors may be more stringent at the later stages of root-hair cell entry involving the formation of infection threads than for induction of earlier symbiotic responses. Hence, there may exist two types of Nod factor receptors—one for “entry” and one for “signaling” (1, 5). In support of this notion is the phenotype of *SYM2A* mutant pea plants and of the *M. truncatula* LYK3 and LYK4 RNAi transgenic lines. The phenotype of these plants is characterized by a block in the formation of infection threads when the plants are inoculated with rhizobia mutants producing altered Nod factors; earlier symbiotic responses appear not to be affected (1).

Future studies should rapidly tell us whether the LysM-containing region of symbiotic LysM-RLKs is directly involved in Nod factor binding and recognition. In addition, we need to know whether the LysM-RLKs need to be assembled into heterodimers in order to bind ligand and activate downstream targets, whether the same heterodimer is both the “entry” and “signaling” receptor, and whether the same two dimer partners are active in the different stages of the symbiotic response and infection.

How do putative Nod factor receptors participate in symbiotic signaling pathways? The NFR1 and NFR5 Nod factor receptors act upstream of the common SYM pathway. Legumes seem able to interact with rhizobia through the specialized ability of certain LysM-RLKs to recognize rhizobial Nod factors and to transduce this signal through the common SYM pathway. One of the SYM pathway genes has been cloned (*STMRK = NORK*) and encodes an RLK with leucine-rich repeats in the extracellular region. In *M. truncatula*, mutations in NORK and in another SYM gene called *DM11* have the same phenotype, which suggests that the encoded proteins form a complex (6) that recognizes bacterial and fungal symbiotic signals. It is not known how the Nod factor receptor activates the NORK-DM11 complex, nor how the common SYM pathway leads to two different symbiotic programs.

The identification of a key role for LysM-RLKs in Nod factor perception is a landmark in our understanding of plant-microbe interactions and in oligosaccharide signaling in plants. The development of genomic approaches in model legumes has been instrumental in this success and will benefit future genome-wide analyses of symbiotic gene expression programs in plants. Gene transfer of the LysM-RLK nodulation genes into nonlegumes will establish whether Nod factor responses can be triggered in these plants and how far the process of nodule formation can go. The finding that LysM domains are involved in the perception of well-defined oligosaccharide ligands should facilitate the dissection of this common protein domain. It may also lead to identification of ligands that activate plant orphan receptors so far identified only in genome sequencing projects.

**References and Notes**

13. We thank D. Kahn and C. Gough for critical reading of the manuscript.

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**Perspectives**  

**Geophysics**

**Glacial Flow Goes Seismic**  

Mark Fahnestock

![Image](https://example.com/glacier-flow.png)

**T**he notion of a large ice sheet is familiar to many through descriptions of the vast expanses of ice that once covered much of Canada, the northern United States, and Scandinavia. It usually evokes a picture of a slowly spreading mass that is nearly inert and rests firmly on the ground beneath. Yet glaciologists tend to see the remaining large ice masses in Greenland and Antarctica as dynamic objects, capable of relatively rapid changes in discharge at outlet glaciers near the ice edge (see the figure).

The time scales for change range from ongoing responses to the end of the last ice age (~10,000 years ago) to changing ice discharge in ice streams (100 to 10 years) to glacier surges that can last from a few years to a few weeks or days. Only the most rapid of observed speed changes occur during a single day.

On page 622 of this issue, Ekström et al. (1) describe the detection of glacially generated seismicity that they attribute to rapid shifts of substantial ice mass over tens of seconds. Previous observations of glacial seismicity involved small events lasting a few seconds, each only meters in extent, that occurred near the ice bed interface and clustered around sites of resistance to ice flow (2). The events documented by Ekström et al. are much larger and may involve shifts of large parts of glaciers and/or the glacier bed, possibly as a result of a short-term failure of the connection between the ice and underlying bedrock.

The long-period seismic signals from these events, generated by a rapid pulse of motion lasting the better part of a minute, show that parts of the ice sheet may accelerate suddenly. It is helpful to place this type of episode in the context of previously observed rapid variations in ice flow. As mentioned above, some glaciers, including outlet glaciers from large ice sheets, are subject to surges that might last a few hours, days, or months (3, 4). Some even alternate between rapid-flow episodes (surges) and near-quiescence. But the possibility that an event that lasts less than a minute may involve tens of cubic kilometers of ice shifting by meters has not been considered before.

Any short-term fluctuations of ice speed must involve changes in rates of sliding over the glacier bed. Large glaciers are known to change speed in response to external forcings, such as water input from melting and ocean tides for glaciers that end in the sea. These forcings can produce large changes in speed over the course of hours to days; the present work suggests that this time scale may need to be extended down to minutes, and the hypothesized mechanisms may need to be modified.

The map of glacier-related seismic activity in Greenland presented by Ekström et al. shows three main clusters of events (1). All three are sites of very large outlet glaciers in areas that are experiencing substantial surface melting. Measurements from a NASA airborne laser altimeter have shown that these glaciers are also undergoing rapid thinning in their lower reaches (5). Rapid