Chapter 5
The Genes and Genomes of the Potato

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Abstract During the last decade, genomics research has generated new insights into potato genetics and made possible new strategies for varietal improvement. The most commonly grown and eaten potato is an autotetraploid, highly heterozygote crop suffering from rapid inbreeding depression. The genetic improvement of the potato presents numerous challenges using conventional tetraploid breeding techniques. However, novel breeding technologies are now available to increase precision and gains for varietal improvement. The public availability of the first potato genome sequence has created new ways to identify the genetic determinants of key traits of the potato as well as ways to use this knowledge for speeding up variety development. Genomic selection applied to tetraploid breeding promises to increase prediction of progeny performance by a more efficient selection of parents. Diploid hybrid breeding is finally making its way two decades after discovering a suppressor gene of the self-incompatibility locus of diploid potatoes. Direct gene transfer into existing varieties of major genes for key traits has been successful but biotech potato development has been constrained by public perception and issues related to the regulation of the technology. Although genome or gene editing is still in its primary stage in potato, it has already been successful in modifying gene expression in a controlled way, and it might face a lower regulatory burden and easier adoption than biotech, transgenic potatoes. Concluding on an optimistic note, we have many reasons, and evidence is starting to mount, that potato crop improvement is finally benefiting from decades of investment in molecular genetics and that the future hold the promises of faster releases of more robust varieties to pest, disease, and climatic extremes, as well as nutritionally enhanced varieties to feed an ever-growing world population.

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5.1 At the Crossroad of Potato Improvement

5.1.1 The Numerous Challenges of Tetraploid Potato Breeding

Potato breeding has a long and successful history of improved variety released after breeding from mostly advanced breeding clones and landraces of tetraploid nature from essentially two genepools, the short-day adapted upland Andigenum and the long-day adapted lowland Chilotanum (Bonierbale et al., this volume; Spooner et al. 2007). The latter group has given rise to the modern cultivar well-adapted to the Northern hemisphere referred to as the Tuberosum group (Gavrilenko et al. 2013). In the US and Canada, variety replacement has been particularly disappointing in potato since turnover is in the range of several decades, unlike grain crops (Walker 1994). In developing countries, there has been marked change in variety adoption as evidenced by a study on CIP-related varieties which grew from nothing to beyond one million hectares in 35 years (Thiele et al. 2008). A more recent study by Gatto et al. (2018) provides further insight on the impact of CIP's breeding efforts, and documents that in China, the world's largest potato producer, there are over one million hectares planted with varieties that trace back to CIP pedigrees. Furthermore, CIP's genetic footprint in China reaches above 35% of all varieties currently in use, be it through the registration of CIP advanced breeding lines as varieties or through using CIP's elite breeding lines as parents in crosses initiated by Chinese breeding programs. The main bottleneck explaining the difference in varietal turnover is market-driven mostly by processing industry in the US and Canada, unwilling to adjust their manufacturing processes to the cooking and frying attributes of the new varieties. Regardless, potato breeding has shown the ability to deliver varieties with market-demanded processing qualities and new traits for higher resilience against climatic extremes, pest and diseases threats, and with enhanced nutritional qualities.

Phenotypic recurrent selection has been the method of choice to select for improved potato lines starting usually with about 100,000 seedlings from 200 to 300 crosses followed by clonal selection over many years (Bradshaw 2009, 2017). A recent review of the history of conventional potato breeding revealed many examples of important varieties been released after 30 years or more of crossing and clonal selection when an optimal timeline should be 13–14 years (Bradshaw 2009; Jansky and Spooner 2017). The main reason for such long cycle for variety development is the quantitative nature of most important traits, the rapid inbreeding depression, and the low intensity of selection in early generations. The propagation through tubers adds on delays due to low multiplication rate and ease of contamination with pathogens which delay bulking enough quality seed tubers for multilocation field selection.

The genetic base of potato varieties grown in large commercial area is relatively narrow compared to the accessible gene pool for conventional breeding of the potato. This is likely due to the narrow genetic base of the original tetraploid sources from Andigenum and Tuberosum which were used as starting material for breeding.

Ellis et al. (this volume) provide a detailed current status of the gene pool and the germplasm of potato. Many wild potato species can be crossed with cultivated potatoes directly or via another wild species used as a bridge (Plaisted and Hoopes 1989). However, only a fraction of useful genes from wild species have been introgressed successfully into modern potato varieties. About 40% of the wild species carry interesting genetic traits value for pests, diseases and abiotic stresses (Sood et al. 2017). Major genes for disease resistance from wild relatives of the potato were introgressed into breeding lines for late blight (*S. demissum, S. bulbocastanum*), viruses (*S. stoloniferum*), and nematodes (*S. spegazzini, S. vernei*) resistance (Bradshaw and Ramsay 2005; Bradshaw 2009; Finkers-Tomczak et al. 2011).

The real contribution of wild relatives to modern potato varieties is likely underestimated due to uncertainty in pedigree information and quantitative nature of many important traits of the potato. *S. acaule,* which has been a source of disease resistance and abiotic stress tolerance but has been more used as a bridge between wild species and the cultivated potato (Watanabe et al. 1992). From the first cross between *S. bulbocastanum* bearing late blight-resistance genes and the bridging wild species *S. acaule*, 46 years of crossing and selection with cultivated potato, first diploid *S. Phureja* and then tetraploid *S. tuberosum*, were necessary to release the late blight-resistant varieties "Bionica" and "Toluca" (Haverkort et al. 2009). Introgression of wild species genomes into the cultivated groups has been facilitated by unreduced (*2n*) gametes in diploid potatoes and was shown to be highest in group Tuberosum because of intense breeding effort using a dozen of wild species (Plaisted and Hoopes 1989; Hardigan et al. 2017). Wild species carry genes for wild characteristics which are introduced as genetic drag with the disease-resistance genes lead to the notion that there could be a tradeoff between disease resistance and yield (Ning et al. 2017). This might have contributed to the limited use of wild species in potato breeding.

Assuming allelic combination has to consider one positive allele from a wild species and three neutral alleles from cultivated potato, the introgression of only ten positive alleles from wild species is only one in a million genotypes [$(1/4)^n$ where $n = 10$ genes]. This number becomes quickly without practical reach considering epistatic effects from the cultivated potato alleles, and that each cross redistributes the 20 or so quantitative trait loci which are priority traits of modern varieties (Bradshaw 2017). Potato being an auto-tetraploid clonally propagated crop has also accumulated rare mutations and epigenetic changes in alleles otherwise identical. This complicates further the straightforward exploitation of emerging molecular breeding approaches (Visser et al. 2014).

Increased selection intensity before clonal selection has been proposed by progeny tests and full-sib family selection (Bradshaw et al. 1995, 2000). Marker assisted selection can also screen at early stage major genes and Quantitative Trait Loci (QTL) with large effects (Gebhardt 2013; Sharma et al. 2014). In recent years, markers flanking major genes and QTL were developed for resistance to viruses (Mihovilovich et al. 2014; del Rosario et al. 2018), tuber starch and yield (Schönhals et al. 2016), and other important traits (Ramakrishnan et al. 2015). If applied at the

early clonal generation stage and multiplexed, marker-assisted selection can be cost-effective (Slater et al. 2013). Estimated breeding value for traits which can be inferred from pedigree information was also proposed to accelerate the intensity of section and result in shorter breeding cycle (Slater et al. 2014a, b). Genomic selection is also proposed to improve combining unknown QTL at an early stage in the breeding process (Slater et al. 2016). New high density and high throughput polymorphic marker systems have been developed for potato (Hamilton et al. 2011; Uitdewilligen et al. 2013; Vos et al. 2015). Using a panel of 83 cultivars of mostly European origin, a high frequency of relatively rare variants and/or haplotypes, with 61% of the variants having a minor allele frequency below 5%, was found which can be explained by the limited number of meiosis separating these cultivars (Uitdewilligen et al. 2013). Recent estimates of linkage disequilibrium in modern potato cultivar populations confirmed the relatively limited number of meiosis separating modern cultivars and therefore limited power of Genome Wide Assisted Studies (GWAS) for allele/gene discovery (Vos et al. 2017; Sharma et al. 2018).

Hence, ways to improve conventional potato breeding exist and are under development but the fundamental inherent limitations of the narrow genetic base of advanced tetraploid potato germplasm used by breeders, the rapid inbreeding depression, and the low multiplication rate of seed tubers call for new methods and tools to improve the potato which will be complementary to conventional tetraploid breeding for some and an alternative for others.

5.1.2 New Potato Breeding Technologies

Potato genetic improvement has taken shortcuts many times to circumvent the limited genepool accessible by crossing and the tedious phenotypic recurrent selection.

Mutagenesis has long been used to improve yield, quality, biotic and abiotic stress resistance, and tolerance of many crops (Maluszynski et al. 1995). According to this review, more than 1,700 mutant varieties involving 154 plant species have been officially released. However, the tedious process of segregating out the rare positive mutation from the negative ones represent a bottleneck for potato crop improvement. Nevertheless, a novel form of doing mutagenesis is making a surprising come-back for potato crop improvement as mentioned below.

Somatic hybridization has been used in potato to bypass sexual incompatibilities between cultivated potato and wild species for about 40 years (Tiwari et al. 2018). These authors reported successful fusion products obtained from 23 *Solanum* species that were characterized for multiple traits. Numerous studies were generated from somatic hybrids to understand the genetic architecture of important traits including isolating important genes. However, no variety has apparently been released from breeding somatic hybrids with cultivated potato likely due to the limitation of tetraploid potato breeding to efficiently remove undesirable alleles.

Although direct gene transfer through transgenics has a much shorter history in potato crop improvement than conventional breeding approaches, it has been

highly successful, though for a limited number of traits for which natural genetic variation was not readily available. Virus resistance was the first trait successfully engineered in potato in the late 1980s, and a commercial cultivar was first reported with the combined resistance to PVX and PVY (Lawson et al. 1990). Soon after, an insect resistance was engineered and led to the production of new commercial cultivars (Perlak et al. 1993). This first generation of biotech potatoes were commercialized under the name of NewLeaf™ from 1995 through 2001 in the United States and Canada, but potato processors and retailers realized soon that the NewLeaf potatoes were going to increase their costs without a share of their benefits which precipitated their decline (Thornton 2003). By 2004, none of them were commercialized anymore. For the next decade, no new biotech potato was released. Recently, a series of potato biotech varieties have been released with reduced bruising and browning first and then with late blight resistance, low acrylamide potential, reduced black spot, and lowered reducing sugars while others are near to be released (see below). The opportunities for engineering new traits that bring benefits to the producer and the consumer are numerous and applicable to potato (Halterman et al. 2016). However, the public acceptance of biotech crops remains volatile and unpredictable, and the current lack of science-based regulatory frameworks in many potato producing countries constrain the scope of genetic engineering to products with sizable benefits to both producers and consumers unachievable by other means.

Genome (gene) editing is the most recent and significant genetic engineering technique targeting specific DNA sequences in the crops' genome (Scheben et al. 2017; Yin et al. 2017). Targeted mutagenesis of specific genes for knock-out, deletion, or allelic changes are now possible with a final product free of foreign DNA. Potato has already been shown to be amenable to genome editing and even to develop novel useful products (Butler et al. 2015, 2016; Clasen et al. 2016; Nicolia et al. 2015; Wang et al. 2015; Andersson et al. 2017; Ma et al. 2017). The two editing tools, TALEN and CRISPR/Cas9, must access the genome without integration of foreign DNA since it cannot be eliminated by crossing without losing most of the qualities of the original commercial variety. Transient expression by PEG-mediated protoplast transfection or Agrobacterium-mediated leaf infiltration generated the intended mutation, but the absence of a selectable agent and somatic variation of plants regenerated from protoplasts can make these strategies labor-intensive. Delivery of the editing reagent may be mediated by virus vectors, but their spread and elimination pose additional difficulties. Hence, genome editing technology offers great opportunities in potato but is still at its first stage of development.

True hybrid potato is a new potato breeding strategy which is increasingly been regarded as the game-changing solution to many of the pitfalls of conventional tetraploid breeding. The sparking step goes two decades back with the discovery of a self-incompatibility inhibitor gene in the wild species *S. chacoense* (Hosaka and Hanneman 1998a, b). The *S* locus inhibitor gene (*Sli*) was introgressed into diploid cultivated potato and shown to confer self-compatibility

(Phumichai et al. 2005). Soon after, few breeding programs started to introgress the *Sli* gene into their diploid potato lines and obtained S3 diploid lines with 80% homozygosity and good agronomic performance including yield (Lindhout et al. 2011). In parallel, an inbred line of *S. chacoense* (M6) was developed to produce recombinant inbred line populations (Jansky et al. 2014). As stated in the title of an opinion paper by a large community of US potato geneticists and breeders, it is proposed to "reinvent the potato as a diploid inbred-based line crop" (Jansky et al. 2016). New sources of self-compatibility system are needed to circumvent the use of the wild species *S. chacoense*. Within the diploid cultivated potato germplasm, self-compatible landraces exist, though rare, but can be used to develop inbred lines from distinct gene pools such as the Stenotomum group and Phureja group (Haynes and Guedes 2018). Recently, an even more promising new system has been developed by knocking out the self-incompatibility gene *S-RNase* using the CRISPR–Cas9 gene editing system (Ye et al. 2018).

In addition to obtaining quick genetic gain by fixing major genes for disease resistance or other important traits and exploiting heterosis by hybridization, the hybrid variety propagation is via true seeds. The use of botanical seeds has long been known to be an extremely interesting alternative to tuber seeds because of it low weight, lower content of pathogens, good storability, option for beneficial coating, and high multiplication rate. Previous work by CIP and other potato research organizations on the concept of True Potato Seed (TPS) aimed to complement traditional seed systems by the use of botanical seed as a mean to propagate potato. However, its actual adoption by farmers has been much less than originally expected. Breeding for good parental clones from tetraploid breeding lines led to the development of several varieties but adoption remained conditioned to reduced or scarcity of seed tuber supply at affordable prices (Almekinders et al. 2009). Recently, a TPS variety, Oliver F1, was developed by the Dutch breeding company Bejo Zaden B.V. (http://www.bejo.com/magazine/bejo-introduces-its-first-true-potato-seed-variety) and is now under deployment in some African countries where quality seed availability is rare. Many years of breeding to develop superior parental inbred lines with disease-resistance genes adapted to the various agroecologies and markets are needed but the potential benefits that could be derived from true hybrid potato seeds are immense. The next decades will tell us whether reinventing the potato as hybrid varieties from diploid inbred parental lines will be adopted by small-holder farmers in developing countries who are the likely first adopters of this new technology.

5.2 The Genome of the Potato

5.2.1 Cultivated, Wild Potato Genome Sequences Towards a Pan-Genome

The identification of the first cultivated potato genome sequence is and will remain a turning point in the history of potato science. Prior to its discovery, genetic markers were associated to genetic determinants of traits breeders and geneticists had been working on. A fraction of the genes was known while transcriptomes were describing their expression in tissues, at different times, and under various environmental situations. Candidate genes were tested for association with these quantitative trait loci but for the most, genes underlying QTL remained unknown. The potato genome sequence brought together all this genetic knowledge into a physical perspective for the first time. Eighty-six percent of the 844 Mb genome was assembled into 12 pseudomolecules where 39,031 protein-coding genes were predicted (The Potato Genome Sequencing Consortium 2011). The potato whose genome was sequenced is a homozygote diploid plant obtained after chromosome doubling of a monoploid derived by anther culture of a heterozygous diploid potato from the *Solanum tuberosum* Group Phureja (Paz and Veilleux 1999). This cultivar groups are diploid short-day adapted cultivars producing tubers lacking dormancy. They occur throughout the eastern slope of the Andes from western Venezuela to central Bolivia at elevation between 2000 and 3400 masl (Ochoa 1990). Other genome sequence from cultivated potato, in particular from the Group Andigenum and Tuberosum including modern cultivars are still missing and expected to reveal insight into the domestication/wild species contributions to the various groups of cultivars. The difficulties lie in the presence of four genome sequences derived by auto-ploidization and multiple introgression of chromosome segments from wild species (Rodríguez et al. 2010; Spooner et al. 2014). This makes assembly and phasing particularly difficult and only recently claims of successful assembly of all four genome sequences from modern potato cultivars were made (*NRGene* at http://www.nrgene.com). The comparison of 99 Mb of genome from a potato of the group Tuberosum with the DM potato genome sequence revealed collinearity and high sequence identity (The Potato Genome Sequencing Consortium 2011). A year after the release of the potato genome sequence, the tomato genome sequence was published together with its closest wild relative and compared to the potato genome sequence (The Tomato Genome Consortium 2012). As known from previous cytological and comparative genetic mapping and synteny studies, the tomato genome presents very similar chromosomal organization but nine large and several smaller inversions. The euchromatic, gene rich regions diverge by 8.7%, whereas the intergenic and repeat-rich heterochromatic regions diverge by 30%. The potato genome sequence was greatly improved by ordering and reordering 93% of the previously assembled genome into 12 pseudomolecules representing the 12 chromosomes of the potato (Sharma et al. 2013). This genome sequence continues to be the sole publicly available genome sequence of a cultivated potato. It is accessible through a friendly

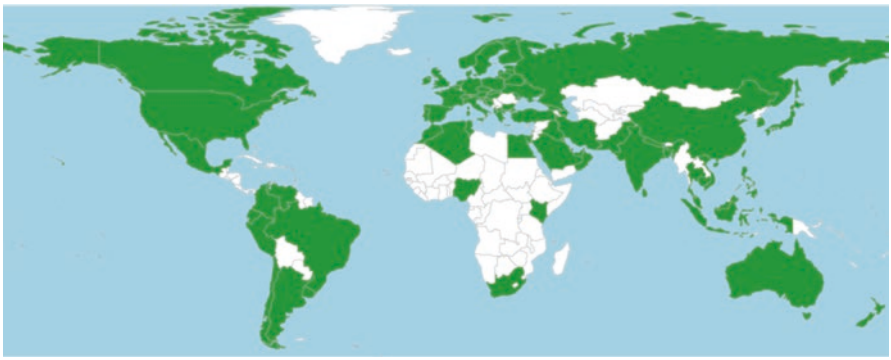

Fig. 5.1 Geographic distribution of SpudDB users. Filled in countries were the source of ten or more unique visits to SpudDB (http://solanaceae.plantbiology.msu.edu/) from October 2017 to October 2018 (Courtesy from John Hamilton, Robin Buell Michigan State University)

web genome browser hosted and maintained by the Buell Lab at Michigan State University in United States and includes annotation datasets, phenotypic and genotypic data from a diversity panel of 250 potato clones (Hirsch et al. 2013). This genomic resource is actively used by potato scientists worldwide (Fig. 5.1).

The initial efforts of the potato sequencing consortium were on resolving the two genome sequences of the dihaploid clone *S. tuberosum* Group Tuberosum RH89-039-16 (RH), but these could not be fully assembled in spite of the availability of the DM sequence. Higher level of heterogeneity was found among the two RH genomes than between RH and DM genomes (The Potato Genome Sequencing Consortium 2011). About 5% of the RH genome sequence (free of repetitive sequences) were aligned with the DM genome sequence and found to be mainly collinear with 97.5% sequence identity, whereas the two RH genome sequences presented 96.5% sequence identity. However, when larger RH genome sequences were obtained, loss of collinearity was frequently observed for the euchromatic region and the three highly diverged pericentric heterochromatin haplotypes of the chromosome 5 (de Boer et al. 2015). These findings stress the importance of sequencing other cultivated potato genome and perform de novo assembly.

Being a diploid and polyploid crop with frequent inbreeding depression and wild species introgression, genome sequence diversity is expected and has contributed to the difficulties of assembling more genome sequences from the cultivated potato.

The genome sequence of a wild species, *Solanum commersonii* was assembled using the potato genome sequence as reference (Aversano et al. 2015). This species has interesting sources of resistance to important diseases of the potato and is known for its freezing resistance and cold acclimation. The species has been used recently in breeding potato for resistance to bacterial wilt in potato and increased levels of resistance were observed (Carputo et al. 2009; Boschi et al. 2017). Flow cytometry estimated a total genome size of 830 Mb. The genome appears to be slightly smaller mainly due to differences in the intragenic regions, to have lower amount of

repetitive DNA, and to have 126 cold-related genes not present in the *S. tuberosum* genome.

Recently, the genome sequence of another wild species was resolved using the M6 inbred clone of *Solanum chacoense* (Leisner et al. 2018). Flow cytometry estimated the genome to be 882 Mb. Using a de novo assembly procedure, 508 Mb of the genome assembly could be used to construct 12 pseudomolecules. These were compared to those of the first published genome sequence and shown with concordance for all of them. Interestingly, the genotype used was a 7-generation selfed *S. chacoense* plant but retained residual heterozygosity on all chromosome with three of them with significantly higher proportion. It is too early to assume that heterozygosity in some region is due either to deleterious alleles or to regions with reduced recombination. Genome annotation for gene-models revealed the presence of 37,740 genes. The *S. chacoense* genome sequence is a new resource for identifying important genes of key traits in population derived from M6.

The pan-genome of the cultivated potato covering traditional landraces (diploids to pentaploids), and modern potato cultivars of the Andigenum and Chilotanum gene pools represents today a huge endeavor due to its extraordinary diversity. When available, it would be a powerful resource for breeders to understand the genome structure of the cultivated potato between the core genome with genes present in all cultivars and the dispensable genome made of genes present only in some cultivar groups. The concept is not restricted to modern cultivars but can include wild relatives, or higher taxonomic level (Vernikos et al. 2015). Clearly, more genomes of wild species are also needed to be assembled to improve our understanding of the interspecific genome variation. Ten years after the beginning of sequencing the potato genome, it is worth noting that only one cultivated potato genome is publicly available unlike maize or rice. This highlights the complexity of resolving uneven heterozygosity of the two or four genomes present in wild and cultivated potato. New sequencing technologies and genome assembly software are about to deliver the genomes sequences from heterozygous potatoes. This is highly desirable due to the diversity of species that have contributed to the potato.

5.2.2 The Genome Plasticity of the Cultivated Potato

Comparative analysis of genome sequences in a small panel of closely related potatoes revealed extensive genome plasticity in potato (Hardigan et al. 2016). This study used a panel of doubled monoploid potatoes derived from *S. tuberosum* Group Phureja landraces with limited introgression from Group Stenotomum, Group Tuberosum, and *Solanum chacoense*. Large regions of the potato genome bearing stress-related gene families are duplicated or deleted revealing a possible evolutionary adaptation response to environmental stresses. Copy number variation (CNV) assessed with a minimum 100-bp size revealed that about 30% of the genes are duplicated or deleted in this panel of 12 closely related potatoes. The duplicated regions varied from 500 bp to 575 kb, with total CNV calls per individual varying

from 2,978 to 10,532 located preferentially in intergenic sequences in pericentromeric region of the chromosomes. This genome plasticity concerns >7000 genes referred to as dispensable genes. A remarkably high level of genome heterogeneity is found in diploid potato, which is retained through clonal propagation.

Genome heterogeneity is responsible for differential gene expression observed among the genes of tetraploid cultivars (Pham et al. 2017). Genome-wide study of genomic variation and transcription in a panel of six North American tetraploid cultivars revealed the importance of preferential allele expression often associated with evolutionarily conserved genes. Additive allele expression genes in leaves and tubers were only slightly more abundant than preferred-allele expression genes. This can be due to the differential presence of regulatory sequences (promoters, enhancers) but also to structural differences (chromatin structure, epigenetic control). Copy number was frequent; about 40% of the genes from each cultivar were in variable copy number. Again here, copy number variation seemed to be more recent and concerning genes involved in response to biotic and abiotic stresses.

Resequencing of the genomes of a representative sample of cultivated potatoes revealed about 2622 genes under domestication selection, with only 14–16% shared by the North American modern potato cultivars and the Andigenum landraces (Hardigan et al. 2017). This relatively small original gene set suggests a relatively short original common domestication of cultivated potato which diverged into two geographically distinct and long-day adapted cultivar groups by the contribution of wild species. An equally plausible interpretation is two independent domestication events from distinct wild species. This hypothesis has been debated since the early days of potato taxonomy at the beginning of the twentieth century opposing the Russian and the English taxonomist schools advocating respectively multiple and single origin of the cultivated potato (reviewed in Spooner et al. 2014). The absence of extant wild species closely related to the ancestor species of the Southern domestication is the weakest support to this hypothesis (Spooner et al. 2012). The Hardigan study revealed the role of specific wild Solanum species in the evolution of the long-day adapted *S. tuberosum* cultivar group and adaptation to upland and lowland distinguishing the Andigenum and Chilotanum groups. However, both cultivated groups presented a significant contribution from the domestication progenitor *Solanum candolleanum* suggesting the differential contribution from wild species occurred after the domestication from the *S. candollearum* progenitor. Considering variants from the regions of introgression of wild species DNA, the nuclear phylogeny resolved the Chilotanum group and modern cultivars as deriving from the Andigenum group. This study brings closer to closure of a century-old controversy on the independent domestication event leading to the Chilotanum group of cultivars.

5.2.3 New Genomic Tools for Potato Improvement

Potato genomic resources are gradually expanding since the availability of the first potato genome sequence from an Andean potato landrace of the Phureja group (Hirsch et al. 2014). Partial genome sequences are available from dihaploid from modern cultivars and fully resolved haplotypes from tetraploid potato cultivars have been recently achieved. Transcriptomes corresponding to these genome sequences and similar ones have been produced under many important developmental and stress conditions.

The exploitation of potato genomic resources in modern cultivar development is mostly exemplified by the use of the Single Nucleotide Polymorphisms (SNP) arrays developed by the potato community (Douches et al. 2014). Several generations of SNP arrays were generated building on the original Infinium 8303 SNP array (Felcher et al. 2012). As listed by Hirsch et al. (2014), the SolCAP array was used to understand variation for glycoalkaloid biosynthesis in wild and cultivated potato, genotype several diversity panels for a retrospective view of North American potato breeding, for a taxonomic alignment, and for genetic structure of European potato cultivars. Since then, it has been used for genetic mapping in populations derived from a diploid inbred parent (Endelman and Jansky 2016; Peterson et al. 2016), genetic mapping of agronomic traits (Manrique-Carpintero et al. 2015), combined with other SNPs to extend its use to European potato breeding germplasm (Vos et al. 2015), assess linkage decay and testing GWAS models (Sharma et al. 2018), and test genetic identity of accessions in genebanks (Ellis et al. 2018).

5.3 From Genomes to the Genes of the Potato

5.3.1 Gene Discovery Facilitated by the Genome Sequence

Genomics-derived strategies for gene discovery have emerged with the availability of high density markers, decrease in sequencing costs, and the increasing power of bioinformatics.

GWAS has the potential to associate markers with regions, genes, underlying the phenotypic variation of trait of interest, and therefore to increase the effectiveness of potato breeding efforts. Unlike marker association studies based on biparental populations, GWAS is not constrained by the performance of one single genotype as the sole source of an allele of interest, and instead it exploits the power of large populations to identify marker-trait associations. A recent review of GWAS in potato highlighted the importance of understanding the structure (kinship) of the population under study (Sharma et al. 2018). Potato populations made of varieties and breeding lines have been studied to establish Linkage Disequilibrium (LD) between adjacent makers. This is an important parameter of the population under study because the shorter it is the higher is the significance of the association. LD

decay in earlier studies were found to present large variation (1–10 cM until equilibrium) depending on the population, the locus, and the type of markers (reviewed in Spooner et al. 2014). The first whole-genome scan of LD decay on a large European potato cultivar population estimated LD decay to 5 cM (D'Hoop et al. 2010), concluding that association studies can be performed at moderate marker densities. Since the advent of SNP arrays, new GWAS have been conducted and revealed the power of this mapping approach over the biparental mapping (Stich et al. 2013). An extended SNP array of the 8303 SolCAP (SolSTW) was used to genotype 569 potato cultivars with 20k SNP markers (Vos et al. 2017). Although this study used a different estimator of LD decay than previous studies, it was found to be in the range of 1.5 Mb for old potato cultivars and 0.6 Mb for those of the second half of twentieth century, values which are compatible with the known limited number of meiosis (5–10) having taken place in the development of these European cultivar populations (Gebhardt et al. 2004; van Berloo et al. 2007). The most recent study using the SolCAP SNP array on a large European cultivar population of 351 tetraploid potatoes estimated LD decay in different regions (short and long arms, and pericentromeric heterochromatin) of each chromosome (Sharma et al. 2018). Again here, their estimates were in the range of 2.73 Mb for euchromatin and 3.27 Mb for whole chromosomal regions. Hence, most studies of LD decay report a modest decay of LD in European potato cultivar populations ranging from 0.6 to 20 Mb depending on the region and chromosome. Interestingly, smaller values of 0.3 Mb in chromosome 4 to 8 Mb in chromosome 8 were estimated for a population of 652 Andigenum cultivars (Berdugo-Cely et al. 2017). The lower distance for LD decay in these native cultivars is expected though a much lower distance could have been anticipated for a population from cultivar domesticated between 8,000 BC and 11,500 BC based on fossil evidence from the dry coast of Peru and south-central Chile (Spooner et al. 2014). It does appear that GWAS in potato can be successful at a modest marker density conferred by current SNP arrays in particular for traits with large QTL effects. However, GWAS alone will not be sufficient to associate markers directly to a specific gene contributing to the trait of interest in potato cultivar populations due to the limited number of meiotic recombination.

Annotation of the potato genome revealed the large family of plant resistance (R) genes discovered by motif sharing (nucleotide-binding site and leucine-rich repeat domain, NB-LRR) with an estimated number per haploid genome of 438 (Jupe et al. 2012). By rescreening the potato genome for NB-LRR target sequences, a total of 755 *R* gene homolog were identified (Jupe et al. 2013). This *R* gene enrichment and sequencing (RenSeq) method was applied to identify markers co-segregating with *R* genes for LB resistance and rapidly clone them (Jupe et al. 2013; Witek et al. 2016; Chen et al. 2018). A derived application of this genome-wide gene discovery is the diagnostic resistance gene enrichment sequencing (dRenSeq) which identifies full *R* genes and their homologs in breeding materials (Armstrong et al. 2018). Combined strategies to identify or clone, multiple resistance genes for diseases such as late blight, viruses, and nematodes will speed up the development of new cultivar with stacked resistance genes.

5.3.2 *Progress Toward Next Generation of Potato Varieties*

The exploitation of the pan-genome of the potato for varietal improvement will increase as more genomes are sequenced and traits phenotyped more accurately in broad germplasm. However, genetic gain will continue to be low in tetraploid breeding though faster and more predictable by the application of genomic selection. New breeding technologies and diploid hybrid breeding can generate unachievable genetic gains by tetraploid breeding.

Direct gene transfer in potato has been successful in generating disease resistance varieties since the early days of genetic engineering (Halterman et al. 2016). Existing widely grown varieties were genetically upgraded by addition of transgenes conferring resistance to pest and diseases, improved processing qualities, and consumer preferences (Table 5.1).

These transgenes produced new pest and pathogen toxins, silenced incoming viruses or endo-genes, or new enzymes for metabolite engineering. After a short life, the first generation of biotech potatoes were withdrawn as reported above. However, a renewed interest of the industry lead to the release of new biotech potatoes in the US (Waltz 2015). A long awaited released came about the same time in Argentina with a PVY virus-resistant potato variety (Bravo-Almonacid and Segretin 2016). With the exception of the latter, all biotech potato released so far were developed by the private sector. Efforts towards future release of late blight-resistant varieties have increased in the last years (Table 5.1). A 10-year research project in The Netherlands developed transgenic and cisgenic potatoes from four varieties with single and multiple *R* genes (Haverkort et al. 2016). *R* gene stacking was shown to confer high levels of resistance in the filed over several seasons (Zhu et al. 2012; Haesaert et al. 2015). One of these was even fully tested for regulatory approval (Storck et al. 2012). This biotech variety, Fortuna, was unfortunately withdrawn from regulatory approval because of the unfavorable European environment. In the US, a 5-year project aimed at the release in Indonesia and Bangladesh of late blight-resistant local varieties with three *R* genes (https://www.canr.msu.edu/biotechpp/index). These three-*R*-gene biotech potatoes are also the focus of a project aiming at release in sub-Saharan African countries potato varieties with an extremely high level of genetic tolerance to late blight, the most devastating disease in potato, caused by *Phytophtora infestans*, unrivalled by the genetic tolerance achieved to date through conventional breeding(Ghislain et al. 2018). Biotech potatoes have been field tested under natural infection for five seasons and have not shown any lesions caused by *P. infestans* (Fig. 5.2).

The latter two projects are benefiting from the release in the US of the Innate potato with late blight resistance for which the regulatory dossier is publicly available (Clark et al. 2014). One of the important costs in regulatory dossier development is the toxicity assessment of the new proteins for which the 3*R* gene technology can build a weight of evidence instead of costly purification, stability, and gavage testing (Habig et al. 2018). Therefore, when both projects estimated their regulatory costs, these were found to be reasonable unlike those reported by

Table 5.1 Traits of biotech potato from potatoes approved for food and cultivation (source ISAAA GM crop database)

Trait(s)	Trade name	Developer	First approved for food	First approved for cultivation
Colorado Potato Beetle resistance[a]	New Leaf™ Russet Burbank potato	Monsanto Co.	CAN USA (1995); AUS JPN NZL (2001); PHL (2003); KOR (2004)	USA (1994); CAN (1995)
	Atlantic NewLeaf™ potato	Monsanto Co.	CAN MEX USA (1996); AUS NZL (2001)	USA (1995); CAN (1997)
	Superior NewLeaf™ potato	Monsanto Co.	CAN (1995); USA (1996); MEX (1996); AUS JPN NZL (2001); PHL (2003); KOR (2004)	USA (1995)
Colorado Potato Beetle and PVY resistance[a]	New Leaf™ Y Russet Burbank potato	Monsanto Co.	USA (1998); CAN (1999); AUS JPN MEX NZL (2001); PHL KOR (2004)	USA (1997); CAN (1999)
	Shepody NewLeaf™ Y potato	Monsanto Co.	USA (1998); CAN (1999); AUS MEX NZL (2001); JPN PHL (2003); KOR (2004)	USA (1997); CAN (2001)
	Hi-Lite NewLeaf™ Y potato	Monsanto Co.	USA (1998)	
Modified starch (high amylose)[a]	Amflora™	BASF	EU (2010)	EU (2010)
	Starch Potato	BASF	USA (2014)	
Low asparagine (acrylamide), low black spot bruise	Innate® Cultivate	JR Simplot Co.	USA (2014); CAN (2016); AUS JPN MEX MYZ NZL (2017)	USA (2014); CAN (2016)
	Innate® Generate	JR Simplot Co.	USA (2014); CAN (2016); AUS MEX NZL (2017)	USA (2014); CAN (2016)
	Innate® Accelerate	JR Simplot Co.	USA (2014); CAN (2016); AUS MEX NZL (2017)	USA (2014); CAN (2016)
Low asparagine (acrylamide), low black spot bruise, late blight resistance	n/a (Russet Burbank)	JR Simplot Co.	USA (2015); AUS CAN NZL (2017)	USA (2015); CAN (2017)
	Innate® Acclimate	JR Simplot Co.	USA (2016); AUS CAN NZL (2017)	USA (2015); CAN (2017)
	Innate® Hibernate	JR Simplot Co.	USA (2016); AUS CAN NZL (2017)	USA (2015); CAN (2017)
PVY resistance	n/a (Spunta)	Technoplant Argentina	ARG (2018)	ARG (2018)

Countries are represented by three letter codes
[a]Refers to products phased out of the market

Fig. 5.2 Confined field trial conducted in Uganda with transgenic potato with three *R* genes (dark green plots), developed as described by Ghislain et al. (2018), and nontransgenic potato varieties (severely damaged plots)

larger players for commodities like maize (Kalaitzandonakes et al. 2006; Schiek et al. 2016). However, the adoption of biotech potatoes remains challenging due to negative perception by a large part of the public unfamiliar with the challenges and potential solutions to improve agriculture production. The long-standing opposition to industrialization of agriculture, the concerns about multinational corporate dominance, the lack of trust in risk assessment of regulatory agencies, the growing conflict of interest of the organic industry, and the fear of unknown manipulations of our food, have delayed the approval and adoption of biotech crops. The release of biotech potatoes addressing a major long-lasting threat on its production which calls back bad memories to Europeans and North Americans, may well result in a perception change provided strong public education is developed (Hallerman and Grabau 2016).

Gene editing in potato has already passed the stage of proof-of-concept as reviewed above. There are yet no potato products on the market, but gene-edited varieties will soon be released with traits governed by known existing genes whose regulation and allele structure determine the trait value (Table 5.2).

It is important to realize that gene editing is a complement to transgenesis, not replacement, because it is limited to the existing endogenous genes of the potato. Disruptive news came up recently when the European Court of Justice passed a judgment that genome edited crops should be regulated using the same regulatory framework as the transgenic crops (Callaway 2018). This decision is reminiscent of a previous one in 2012 when the European Food Safety Authority concluded that cisgenic crops should be regulated as transgenic crops (EFSA 2012). This European

Table 5.2 Traits targeted by genome editing in potato and opportunities for improving pest and disease resistance as well as nutritional qualities of the potato

Trait	Target gene	Expected impact	References
Heat tolerance (high yield under higher temperature)	Heat-shock cognate 70 (HSc70)	Enhanced yields of potato grown under lowland tropics	Trapero-Mozos et al. (2018)
Virus resistance (PVY potyvirus resistance)	Eukaryotic translation initiation factor 4E (eIF4E)	Reduce yield loss due to PVY and enhance tuber seed quality	Arcibal et al. (2016)
Reduced accumulation of reducing sugars	Vacuolar invertase (VInv)	Improved qualities of processed potato	Clasen et al. (2016)
Reduced acrylamide in processed products	Vacuolar invertase gene VInv and the asparagine synthetase genes StAS1 and StAS2	Reduction of acrylamide formation under extreme cooking temperature	Zhu et al. (2016)
Decreased accumulation of glycoalkaloids	Sterol side chain reductase 2 (St-SSR2)	Release of advanced breeding potato lines with elevated SGA	Sawai et al. (2014)
Inbreeding tolerance	S-RNase alleles (Sp3 and Sp4)	Generation of self-compatible diploid potato for developing hybrid potato varieties	Ye et al. (2018)
LB resistance	Ethylene response factor StERF3; 6 susceptibility genes; DND1 gene	Reduction of production losses and reduced costs of production	Tian et al. (2015), Sun et al. (2016a, b)
VitA biofortification	beta carotene hydroxylase *b-ch* gene	Enrichment in beta carotene in potato (precursor of VitA)	Van Eck et al. (2007)

decision will impact agricultural biotechnology innovation negatively not only in Europe but also in developing countries.

Hybrid breeding in potato has already been tested by farmers in developing countries and has received great excitement by the potato crop improvement actors in spite of the initial skepticism (Lindhout et al. 2017). The first yield assessment of hybrid varieties was conducted in two locations; the Netherlands and the Democratic Republic of Congo (de de Vries et al. 2016). In the latter, the best hybrid variety yielded three to four times the national average in sub-Saharan Africa (SSA) countries, whereas it yielded only half of the yield of conventional varieties in the Netherlands. A confounding factor is the type of seeds and health status that will need to be factored out for more precise yield comparison between hybrid and conventional potato. Nevertheless, the possibility of combining complementary traits from the parents, obtaining heterosis from hybridization of inbred parents, avoiding pathogen load of seed tubers, and facilitating transport of true seeds leaves no doubt that hybrid varieties will attract a lot of interest in the developing world.

5.4 Concluding Remarks

Despite early optimism, and unlike in other crops, the vast insight gained from its genes and genome has not been steadily translated into substantial genetic progress in potato, through either molecular breeding or transgenic approaches. Among the issues behind the above, the genetic complexity of tetraploid potatoes, issues related with public acceptance of transgenic crops, and a critical mass smaller than in other crops stand out as the most salient ones. Regardless, we remain confident that recent scientific developments, such as an increased focus on developing hybrid varieties at the 2X level, are one of the main factors that will change the above-described trend, since a main advantage of dealing with 2X instead of 4X genetics is a much more straightforward application of molecular approaches, as demonstrated already by the routinary use of such technologies in other Solanaceous crops such as potato, and to a lesser extent, pepper. In addition, early reports on the use of genomic selection in potato have demonstrated its ability to circumvent many of the pitfalls observed when QTL were used to attempt increasing the effectiveness of potato breeding efforts. The continuous reduction of DNA sequencing will enable collecting sequencing data on a larger scale than before, further facilitating both the identification of genomic regions associated with traits of economic importance, and a better understanding of quantitative traits in potato. Regarding the use of gene editing approaches, although they provide a much more targeted ability to modify the potato's genome, the full realization of its potential to facilitate the development of varieties carrying genetic alleles not hitherto found in the germplasm available will, by and large, depend on how the public acceptance of genetic modification evolves, both in developed and developing countries.

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