Review

Genomic-Led Potato Breeding for Increasing Genetic Gains: Achievements and Outlook

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ABSTRACT

Potato is the third most important crop, after rice and wheat, in human diets worldwide. Genetic gains due to its crossbreeding for productivity *per se* appear to be stagnant in this tetraploid crop. Its genetic enhancement needs to overcome inherent barriers such as ploidy, outcrossing and heterozygosity. Pathogens and pests affect potato because they may infect the entire plant, including stems, leaves and tubers, thus leading to significant tuber yield loss. Hence, host plant resistance breeding remains key for improving the productivity of this crop. This article reviews recent research advances relevant to potato breeding emphasizing genomic resources, methods and tools for genetic analysis, mapping of genes and quantitative trait loci, and genomic prediction of breeding values (or genomic selection) for population improvement. In this regard, association genetics has provided insights onto genetic architecture and inheritance of priority breeding traits, as well as tagging them to DNA markers for their further use as aids for indirect selection. Early research results show the feasibility of genomic selection as a new breeding approach for a tetrasomic polyploid such as potato. This manuscript also highlights the proposed inbred line strategy for producing diploid F_1 true potato seed hybrids, and how its use may speed up and increase genetic gains in potato breeding; as well as promoting alleles through gene editing. The paper ends proposing a new interploidy breeding approach considering ploidy manipulations and incorporating genomic selection and gene editing for both population improvement and cultivar development.

KEYWORDS: *Solanum tuberosum*; cultivar development; F_1 true seed hybrid; gene editing; genomic selection; heterosis; polyploidy; tetrasomic inheritance

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INTRODUCTION

The tetraploid ($2n = 4x = 48$ chromosomes) potato (*Solanum tuberosum* L.) is the third most important food crop but its global trading only includes a small share (7% in 2017) in fresh, frozen or seed markets [1]. This crop was domesticated about 10,000 years ago in Perú [2], although

there are some evidences on the use of potato peels for food in southern Utah and south-central Chile nearly 13,000 years ago [3]. Research on sequencing the genome of the potato (landraces and cultivars) and its wild relatives reveals a great genetic variation and signatures of selection of genes controlling domestication traits [4]. It was also noticed key wild introgressions after polyploidy, thus taking wild alleles outside their geographic origin. Likewise, it seems that a few genes drove the early improvement of potato as well as that distinct loci were involved in the adaptation of both upland (*S. tuberosum* group Andigena) and lowland (*S. tuberosum* groups Chilotanum and Tuberosum) groups.

Two potato introductions were brought, after Columbus voyages, from South America to Europe in the 16th Century and a few cultivars were grown therein in the 18th century [5]. Selection among seedlings (derived from true seed found in naturally set berries) from established virus-infected potatoes led to increasing the number of cultivars grown in the late 18th and early 19th centuries [5]. Late blight (caused by the oomycete *Phytophthora infestans*) eliminated most of these cultivars in the mid-19th century, thus reducing Europe's potato breeding gene pool. Thereafter new introductions (mostly from Chile) and their crossbreeding with the few surviving European cultivars led to increasing variation through the release of newly bred cultivars in the early 20th century in the northern hemisphere. During the 20th century several collecting trips for potato germplasm (native cultivars and wild species) were undertaken throughout Latin America with the aim of evaluating and using in crossbreeding such genetic resources for broadening the genetic base of the cultigen pool. It seems, however, that the many of the genes bear by most of modern bred cultivars trace to cultivars already grown in the early 20th century, thus suggesting a limited inbred gene pool.

Pedigree information allows assessing relatedness among cultivars and breeding clones, thus facilitating the crossing design among them and increasing the power of association genetics analysis. Coefficients of co-ancestry are derived from pedigree analysis to quantify relatedness among genotypes. Knowledge on pedigrees is also used for naming genes (particularly for host plant resistance) and tracing their identity. Hence, an online pedigree database with a web-accessible interface became available more than one decade ago with the aim of including all cultivars released worldwide and their parents [6]. Moreover, worldwide pedigree analysis over time reveals that the use of elite parental germplasm in crossbreeding led to developing outstanding potato cultivars [7]. Further analysis with single nucleotide polymorphisms (SNPs) found conserved genome segments bearing target genes from an elite parent in its derived offspring following five generations of selective breeding. SNPs are also useful for checking pedigree records in potato [8]. This pedigree-based research along with DNA fingerprinting also allows to identify genome segments that bear important genes related to target traits, thus

facilitating potato breeding-by-design. Hence, it will be worth characterizing with SNPs any newly released cultivars.

Potato breeding nowadays faces several global challenges; i.e., delivering enough and quality food for the diets of a growing human population, fitting newly bred cultivars into sustainable farming, and offering a supply of bio-sources for the agri-food industry [9]. This article provides an overview on the advances in genomic-led breeding for potato, including its main achievements.

GENETIC GAINS IN POTATO BREEDING

Potato is a highly heterozygous, tetrasomic polyploid due to its four homolog chromosomes rather than two in diploid species, thus making its genetics complex [10]. The main breeding objective for this crop remains combining table or processing tuber quality with host plant resistance to many pathogens and pests affecting potato elsewhere, and suitable for being grown and stored. A recent breeding objective to address policy regarding sustainable intensification of potato farming is input-use efficiency to reduce the utilization of fertilizers and watering. Newly bred resilient cultivars are also necessary for growing potato under the changing climate, particularly in heat- and drought-prone sites. The fresh markets for table potato ask for cultivars whose tubers show a nice visual aspect (i.e., shape, depth of eyes, skin and flesh color) and cooking suitability, while the processing markets give priority to tuber chemical composition, particularly for low reducing sugars and appropriate specific gravity (or dry matter content). More recently, the potato industry is also asking for starch quality (amylose: amylopectin ratio), bioactive compounds such as antioxidants, micronutrients (vitamins, Fe, Zn) and the relative ranking of carbohydrates as measured by the glycemic index; i.e., how fast food causes increases in blood glucose levels.

The main benefits brought by bred cultivars include increase incomes due to more tuber yield, decrease of pesticides owing to host plant resistance, and—last but not least—convenience food with enhanced quality for healthy diets. Crossbreeding is still the main approach for developing new potato cultivars and sometimes using its wild *Solanum* relatives that are available in gene banks worldwide. Population improvement with progeny testing may improve the rate of improvement in potato breeding. Selecting desired genotypes to become new potato cultivars is a challenging and time-consuming breeding task. Ploidy manipulations (scaling down and up chromosome numbers) and biotechnology (tissue culture, genetic engineering and genomics) offer means for accelerating the genetic enhancement of this crop.

Genetic gains for potato breeding in the USA since the late 19th century until the early 1990s were noted only for early maturity and overall tuber appearance but not for tuber yield *per se*, while chip-processing ability and dry matter content improved only for white-skin cultivars [11]. These findings relate to the end-users needs. For example, early maturity

cultivars allow widening harvest periods and fitting into profitable "market windows". Likewise, tuber quality traits are priority for table and processing potatoes. The lack of improving tuber yield *per se* could ensue from its negative correlation with maturity [11], the challenge of combining it with tuber quality (often differing as per the needs of growers, processors and consumers) and host plant resistance to various pathogens and pests [12], and its narrow genetic base due to a high degree of relatedness among released cultivars [13]. As advocated by Slater et al. [14], best linear unbiased prediction (BLUP) for selecting low heritability traits—such as tuber yield or quantitative scab resistance—may increase genetic gains, particularly when using phenotypic recurrent selection and progeny testing, or visual selection in early generations. BLUPs—a standard in animal breeding—uses pedigrees and phenotypic values of all relatives to estimate breeding values or the genetic merit for selection candidates. Trial sites from the target population of environments and years of testing may be included in BLUPs as fixed effects to improve the analysis accuracy.

The highly heterozygous tetrasomic potato shows inbreeding depression for several traits upon selfing. Its polysomic inheritance and high heterozygosity provide means for being very productive and stable across environments [15], although both make difficult crossbreeding. Tetraploid potato may show a high degree of intra- and inter-locus interactions when having four distinct alleles, thus resulting in high tuber yield [16,17]. Genomic analysis indicates, however, that tetra-allelic loci are rare in successful potato cultivars [18]. Although, recessive mutations are, noted less frequently, tetraploidy and vegetative propagation explain genetic load or accumulating recessive deleterious alleles in potato. Very recently, Zhang et al. [19] provide some insights about the genetic basis of inbreeding depression, which reduces fitness among the progeny of potato. Pericentric regions in chromosomes bear many deleterious mutations, while regions with high recombination rates carry deleterious alleles for survival and growth vigor. Such a knowledge provides means for designing potato inbred lines by removing deleterious alleles through crossbreeding.

Ploidy manipulations—scaling down with haploids and up with 2*n* gametes the chromosome numbers [20]—offer other useful approach for broadening the genetic base on as well as for expanding *Solanum* germplasm utilization in potato breeding. Wild relatives and diploid landraces are genetic diversity sources captured by crossing with haploids (or sporophytes with the gametic chromosome number; i.e., $2n = 2x = 24$ chromosomes) derived from adapted tetraploid cultivars. Thereafter, haploid-species hybrids ($2n = 2x = 24$ chromosomes) producing gametes with the sporophytic chromosome number (or 2*n* gametes) will transmit this genetic diversity to the adapted tetraploid cultigen pool. The endosperm balance number (EBN), which is an endosperm dosage system requiring a 2:1 maternal to paternal contributions for proper seed

development [21], ensures that only tetraploid offspring arises from sexual polyploidization through 4*x*–2*x*, 2*x*–4*x* and 2*x*–2*x* crossing schemes.

GENOMIC RESOURCES

In this century, potato germplasm enhancement (or pre-breeding) moved from evaluating (or phenotyping) traits in crop wild relatives or landraces into tracking genome sequences to further incorporating them into the cultigen pool [22], particularly host plant resistance and tuber quality for processing. Hence, the focus of germplasm seems to be shifting for introgression of alleles rather than traits *per se*, which is facilitated by using genomic resources and tools. Indeed, DNA sequencing and genetic markers allow tracking efficiently the incorporation of rare and recessive alleles. Furthermore, the use of DNA marker-aided breeding expedites transfer of major genes while reducing linkage drag. Last but not least, DNA sequences makes easy to find allelic variants for further targeting through gene editing.

The potato genome sequence was the first for an asterid and provided means for revealing 2642 genes that are specific for this angiosperm clade, e.g., those related to tuber biology [23]. The sequencing of a heterozygous diploid clone also confirms deleterious mutations are frequent and may be the basis for inbreeding depression [23]. Genome resequencing shows that potato populations may differ significantly in gene copy number [24]. Further sequencing of landraces, modern cultivars and herbarium samples reveals that potatoes grown in Europe from 1650 to 1750 were related to landraces from the South American Andes, while thereafter potatoes admixed with landraces from Chile [25]. The potatoes grown in Europe in the 19th Century had genes that seem to be involved in long-day pre-adaptation, e.g., the *CYCLING DOF FACTOR1* (*StCDF1*) gene controlling tuberization under long days by unblocking the *SELF PRUNING 6A* (*SP6A*) pathway. The adaptive variant *StCDF1* could arise *de novo* in Europe.

About three decades ago, Bonierbale et al. [26] put together the first potato genetic map based on restriction fragment polymorphisms (RFLPs) using a F_1 segregating population derived from crossing two heterozygous genotypes: a diploid landrace and a haploid-wild species hybrid. Synteny research revealed a high RFLP alignment with the tomato map. Since then other potato maps based on RFLPs or other DNA markers became available [27] and were used for mapping genes and quantitative trait loci [28]. Co-dominant single nucleotide polymorphism (SNP) became available as high throughput genotyping aids for potato genetic research and breeding [29]. They proved to be very useful for establishing relationships among market types [30]. Furthermore, an Infinium 12K SNP V2 Potato Array was used to determine the genetic identity of the accessions held at the gene bank of the Centro Internacional de la Papa (CIP, Lima, Perú) and to assess their genetic diversity, to establish inter- and intraspecific relationships among them, and to define population structure as well as hybrid origins [31]. Likewise, other Infinium 20K SNP

array facilitated the understanding of potato breeding history by identifying “footprints” such as introgression segments plus selection and founder signatures after analyzing cultivars and breeding clones [32]. Founder effects and selection are the most significant for changing allele frequency in potato. Genetic variation located on specific chromosomal regions enabled the finding of SNPs related to host-plant resistance genes, which belong to a large highly variable gene family. Moreover, this assessment demonstrated that genetic erosion is almost absent in tetraploid potato; i.e., 96% of genetic variants found in ancestral cultivars are polymorphic in modern cultivars. DNA polymorphism analysis suggests that modern potato cultivars from Europe and North America are as diverse as the South American landraces [33]. Population structure research in a set of tetraploid cultivars (taken as a sample of 20th century potato breeding history in Europe did not reveal any distinct clustering [34]. This finding indicated that population structure was ignored when selecting the parents for potato crossbreeding. Nonetheless, population structure should be included in association genetics research to avoid any bias when modeling the DNA marker–quantitative trait relationships.

ADVANCES IN METHODS AND TOOLS FOR GENETIC ANALYSIS IN A TETRASOMIC POLYPLOID

Genetic analysis—facilitated by software and algorithms for disomic bi-allelic organisms—are easily used elsewhere but limited for polysomic polyploids showing multi-allelic loci. The disomic inheritance approach is, however, not easy applicable to the tetrasomic genetics of potato because of double reduction and having gametes carrying alleles identical by descent. Furthermore, multiple crossing over affect differently recombination frequency in diploids and polysomic tetraploids [35]. Although the mean frequency of crossing over may not increase, tetraploids appear having greater recombination frequency than diploids. Hence, methods and tools (including algorithms and related software) relevant for genetic analysis in tetrasomic potato became recently available online (sometimes free) for haplotype inference and epistatic detection [36,37], gene dispersal plus population structure [38], relationship matrices and kinship coefficients [39–41], genotype calling (including allele dosage from bi-allelic marker data, e.g., SNPs) [42–44], recombination fractions and haplotype phasing [45], linkage disequilibrium decay and the factors affecting it [46,47], identifying double reduction regions that increases with distances from the centromeres [48], high- or low-density linkage maps [49,50], mapping genes or quantitative trait loci (QTL) [51], and genome-wide association mapping [52]. These and other tools [53] allow getting basic knowledge on genetic architecture or insights on trait inheritance, identifying genes and QTL and tagging them to DNA markers for further use as aids for indirect selection in potato breeding, and developing models for genomic prediction of breeding values for selection. They also increase accuracy in genetic analysis due to

its statistical power vis-à-vis available methods based on disomic inheritance, thus improving estimates relevant to achieving genetic gains while breeding tetrasomic potato.

MAPPING GENES AND QUANTITATIVE TRAIT LOCI FOR DNA MARKER-AIDED BREEDING

Tetrasomic inheritance offers the possibility of having up to five genotypes (instead of three as in disomic inheritance: *AA*, *Aa*, *aa*) for bi-allelic loci; i.e., nulliplex (*aaaa*), symplex (*Aaaa*), duplex (*AAaa*), triplex (*AAAa*) and quadriplex (*AAAA*), and these terms indicating the number of dominant alleles: from none to four, respectively. Furthermore, the two genes in the gamete of a tetrasomic polyploid may derive from different chromosomes in the zygote or identical because originate from same chromosome due to double reduction (α). This results when the sister chromatids end in same gamete owing to homologous chromosomes forming a quadrivalent and thereafter a crossing over occurring between the locus and spindle attachment. Double reduction, which depends on the distance from the centromere, causes segregation distortion in tetrasomic linkage analysis. Sir Ronald Fisher [54] provided the statistical theory of linkage in polysomic inheritance, while Luo et al. [55] gave an update for tetrasomic polyploids considering dominant and codominant markers, as well as allelic dosage, segregation distortion, mixed pairing in meiosis, and incomplete marker phenotype data. Bourke et al. [56] described further an approach for developing genetic linkage maps with large number of markers in a tetrasomic species, and validated it using data from a F_1 segregating population of tetraploid potato, whose 235 individuals were genotyped with a 20K SNP array and after converting SNP intensity values to allele dosages. The resulting potato linkage map included 6910 markers across the 12 potato chromosomes and with a total length of 1061 cM. The use of mono-parental parthenogenetic haploids derived from tetraploid cultivars after prickle pollination with the diploid *S. tuberosum* Group Andigenum (Phureja), permits also mapping genes and quantitative trait loci with single-dose markers in potato, as demonstrated recently [57]. The total length of these genetic maps was 2675.6 cM and having on average 55.24 SNPs per linkage group.

Throughout the 1990s genetic maps based on low throughput DNA markers, isozymes and genes controlling morphological traits became available for diploid potatoes [58]. Host plant resistance genes (particularly for cyst nematode, late blight and viruses), tuber traits (skin color, shape) and flower color were among the traits included. Linkages maps based on SNPs from two diploid populations were further put together to validate the assembled potato genome sequence [59] and the functionality of an Infinium Potato Array. These maps included 4400 markers and covering up to 88% of the genome sequence. A F_2 segregating population derived from crossing two potato diploid inbred lines were also used for genetic mapping of tuber color (skin and flesh), pigment,

shape and length/width ratio; eye tubers (from where sprouts grow); "jelly end" (related to high concentration of reducing sugars and low starch content, and producing tubers instead of sprouts at the eyes of tubers), and anther development [60]. Other alike F_2 offspring facilitated recently the mapping of QTL for tuber quality traits (shape plus flesh and skin color) [61]. The use of F_2 or recombinant populations derived from inbred lines likely allows a precise major gene location and increases the resolution of QTL mapping.

Tetraploid segregating offspring were used along with software for linkage analysis in tetrasomic species [62] for mapping flower color, foliage maturity, plus tuber traits such as skin texture, specific gravity (SG), dry matter content (DMC) and yield in potato [63]. An interesting finding was to identify different QTL that did not co-locate for DMC ad SG, which are strongly correlated. Research in other tetraploid populations led to identifying 41 QTL for high value traits such as fried chip color (after 5.5–7.2 °C storage), as well as tuber yield, number per plant, weight and size [64]. It is worth noting that a QTL for tuber weight, length, and width co-localized with a QTL for foliage maturity on chromosome 5. Progeny derived from crossing a susceptible cultivar and a resistant breeding clone (both tetraploids) were genotyped with an Infinium SNP array and phenotyped for internal heat necrosis [65]. Significant QTL accounting 28.21% and 25.3% of the variation for incidence and severity, respectively, were found on chromosomes 1, 5, 9, and 12. Very recently, the genetic analysis of a tetraploid segregating F_1 offspring facilitated the mapping of a host plant resistance gene to cyst nematode derived from the wild diploid species *S. multidissectum* at the distal end in the short arm of chromosome 5 [66]. These and other alike research provide insights on the genetics of target traits and may allow finding interesting high throughput DNA markers that should undergo further testing to demonstrate their suitability for aided breeding through indirect selection in potato.

There are various resistance (*R*) genes that co-evolved with *P. infestans* in central Mexico—its center of origin and provide high levels of race-specific resistance. The proteins coded by *R* genes target the avirulence (AVR) proteins that are included among the RXLR class effectors secreted by the pathogen [67]. The availability of genome-wide catalogs of these effectors accelerate the cloning of *R* genes and assist on their deployment while monitoring the pathogen strains. For example, eight *R2* gene homologs (with specific response to AVR2) were cloned in the Swedish potato breeding clone SW 93-1015 [68], whose genotype is simplex for this trait. Resistance gene enrichment and sequencing allows finding and annotating pathogen resistance gene in the plant genome [69], thus paving the way for developing co-segregating DNA markers for target trait or accelerating the cloning of *R* genes from *Solanum* species that belong to the NB-LRR type.

Various research articles about host plant resistance QTL for late blight are available since the 1990s. They often relate to late foliage maturity and

are based on phenotyping the disease development in potato. A dynamic phenotyping approach at consecutive time points during disease development (that reflects genes functioning at different stages during the host plant-pathogen interaction) was able to identify six QTL (one each on chromosomes 2, 7 and 12 plus three on chromosome 9), while only one QTL was found using the former [70]. This approach may allow targeting genes or QTL for developing DNA markers for aided breeding. The gene *Rpi-phu1* gene, which derives from diploid species of *S. tuberosum* Group Andigenum and proximal to marker allele $GP94_{250}$, provides a high level of host plant resistance to late blight in potato and it appear to be very suitable for marker-aided selection in diploid and tetraploid potatoes [71]. Likewise, a polymerase chain reaction-based DNA marker serves for tracking and selecting *RB* gene from the wild related species *S. bulbocastanum* [72], which gives broad spectrum, high level of host plant partial resistance to late blight and to which different strains of *P. infestans* are uncapable to overcome quickly [73]. Resistance QTL may be further related to the potato reference genome, in which major nucleotide binding, leucine-rich-repeat (NB-LRR) resistance genes (often from wild species) are known. For example, broad-spectrum, durable, field resistance provided by QTL dPI09c is due to the NB-LRR gene *R8* [74], which recognizes Avr8 and is homologous to the NB-LRR protein Sw-5 found in tomato, as shown recently [75]. The EU cultivar "Sarpo Mira", along with US cultivars "Jacqueline Lee" and "Misaukee" and cultivars PB-06 and S-60 from China, carry this *R8* gene, thus showing its worldwide use in potato breeding. Pyramiding host plant resistance genes is the best strategy to achieve durable host plant resistance to late blight, thus increasing the lifespan of potato cultivars bearing them.

Association or linkage disequilibrium mapping seeks relationships between genotypes and phenotypes in a set of individuals rather than using biparental crossing to generate a family with known relatedness—thus, sampling only few alleles of the species—although both are complementary [76]. D'Hoop et al. [77] suggest, after phenotypic analysis, that results from a single-year balanced field trial along with breeders' records (across sites and over years) provides suitable data for a genome wide association study (GWAS). Mixed-model association mapping considering a kinship matrix seems to be very appropriate for detecting QTL in potato [78]. Really, GWAS allows identifying genomic regions or genes that are very relevant for breeding this crop, e.g., host plant resistance to pathogens [79–85], foliage maturity [79], chip quality plus tuber starch content and yield [86–88], other tuber quality traits [52,89] and marketable tuber yield plus size and number under drought [90]. This association mapping research provided insights in the genetics of various characteristics and led to identifying suitable diagnostic DNA markers for indirect aided selection of target breeding traits in potato (Table 1). A R package based on the Q + K mixed model—known as GWASpoly—has facilitated genome wide association research in polysomic polyploids such

as potato [52]. This software allows modeling various types of polysomic gene action, such as additive as well as simplex and duplex dominant. Its further use also indicated that DNA marker density and population size may limit association mapping in tetrasomic potato. The marker density should indeed surpass the linkage disequilibrium decay for GWAS. Sound experimental design (e.g., incomplete blocks with a minimum of three replicates) for multi-site testing over years or cropping seasons allows adequate field phenotyping of quantitative characteristics, which are often affected by the genotype × environment interaction. Selecting germplasm that maximize diversity and with appropriate relatedness levels will be also key in association genetics. These factors along with high-throughput dense DNA markers, such as SNPs, determine the power for identifying QTL in potato.

A non-statistical alternative method for discovering genes is graphical genotyping [91], which visualizes haplotype sharing in association panels among individuals that also share the same locus, as well as facilitates noticing the linkage drag of introgression segments in breeding populations [92]. Genotype-by-sequencing also provide means for identifying with accuracy genes under selection in the highly heterozygous tetrasomic potato cultivars [93].

Table 1. Genome-wide association study examples in potato.

Characteristic	Most Important Finding(s) in Reference Population	References
Host plant resistance to late blight and plant maturity	Highly significant quantitative trait loci (QTL) related to PCR-based markers specific for major gene *R1* and anonymous PCR markers flanking the *R1* locus at 0.2 cM in tetraploid cultivars from America (North and South), Asia and Europe bred between 1850 and 1993	[79]
	9 single nucleotide polymorphisms (SNPs) significantly associated with maturity corrected resistance (MCR) and accounting for 50% of its genetic variance in tetraploid German breeding clones (main association with *StAOS2* locus encoding allene oxide synthase that is a key enzyme for jasmonate biosynthesis—a plant hormone involved in defense signaling)	[82]
	27 SNPs with significant association with MCR related to strong candidate genes for quantitative resistance in German breeding clones according to functional annotation (being most important: a lipoxygenase (jasmonate pathway), a 3-hydroxy-3-methylglutaryl coenzyme A reductase (mevalonate pathway), a P450 protein (terpene biosynthesis), a transcription factor and a homolog of a major gene for resistance from diploid *Solanum venturii*)	[83]

Table 1. *Cont*.

Characteristic	Most Important Finding(s) in Reference Population	References
Host plant resistance to late blight	Two nucleotide binding-site markers targeting resistance-analog genes with potential for aided-selection in Dutch cultivars	[80]
	16 organ-specific QTL (6 for leaf resistance and 10 for stem resistance, respectively) accounting between 13.7% and 50.9% of the phenotypic variance in diploid *S. tuberosum* Group Phureja (11 candidate genes out of 16 QTL coding for diverse proteins including a leucine-rich repeat kinase)	[84]
	SNP on chromosome 9 significantly associated but linked to instability in a tropical highland breeding population; i.e., AACC or AAAC highly resistant in some sites, while AAAA moderate stable resistance across sites	[85]
Verticillium wilt resistance	Allele of the STM1051 marker accounts > 10% and 25% of the phenotypic variation in two sub-populations based on co-ancestry of tetraploid North American cultivars	[81]
Tuber quality traits	69 significant amplified fragment length polymorphisms associated to 11 traits throughout the genome of a subset of worldwide available germplasm, thus showing the potential for association mapping using available phenotypic data, modest number of DNA markers, and relatively simple statistical analysis	[89]
	Robust and significant associations between DNA variants and genes encoding enzymes participating in starch and sugar metabolism or transport in German tetraploid cultivars and breeding clones User-friendly PCR assays for specific candidate gene alleles useful for marker-aided selection of chip quality after cold storage and tuber starch content	[87,88]
Tuber cold sweetening	Leucine aminopeptidase role in natural quantitative variation of tuber starch and sugar content and their interconversion in tetraploid German cultivars and breeding clone	[86]
Tuber shape and eye depth	Significant QTL for both tuber shape and eye depth on chromosome 10	[52]
Tuber number, size and weight under drought stress	Significant SNP–tuber trait associations in region of chromosome 3 for European tetraploid cultivars	[90]

GENOMIC PREDICTION OF BREEDING VALUES FOR FURTHER USE IN SELECTION

Genomic selection (GS) relying on estimated breeding values (GEBV) offers an approach that increases efficiency and accelerates breeding [94]. GS captures the simultaneous effects of dense DNA markers spread throughout the genome, and it allows predicting breeding values assuming linkage disequilibrium among trait polymorphisms and

markers. A training set from the population (TP) is used for genotyping and phenotyping with the aim of getting GEBV using statistical modeling. Thereafter, the GEBV are used to predict the worth of individuals from a breeding population (BP), in which they are only genotyped but not phenotyped.

In polysomic polyploids accounting for allele dosage (i.e., the additive effect of multiple copies of same allele) may improve prediction accuracy [95,96], thus increasing genetic gains from GS, particularly when a large number of genes with small individual effects affect target breeding trait(s). Polyploidy, heterozygosity, linkage disequilibrium decay, marker number, reference population plus its effective size (that should consider the high allelic diversity due to polyploidy), and trait heritability also influence in tetrasomic potato the accuracy of GS [97], whose genetic gains appears to be above those of pedigree or phenotypic selection. Sverrisdóttir et al. [98] further indicated that combining additively genomic prediction models across TP may yield high quality GEBVs that could be relevant for GS in related BP.

Genomic prediction models for selection became available in various potato breeding populations and for several traits such as starch content [99,100] and yield [99], tuber DMC or SG [96,98,101], chipping quality determined by the fry color [96,98,99], total tuber yield and its components such as number and size [96,100,101], tuber flesh color [101], stems per plant [101] and host plant resistance to late blight [100,102] and common scab [102] (Table 2 gives details for each of these traits). Such encouraging results show that GS based on GEBV may become a feasible breeding approach in tetrasomic potato. It worth highlighting that GS accuracy, as noted in some of the above cited research, relates directly to trait heritability that may be low due to significant non-additive genetic effects [103]. Hence, including these non-additive (dominance and epistatic) effects may improve the genome-wide prediction accuracy, particularly when using it for selecting low-heritability traits in early clonal generations. In this regard, Bradshaw [104] proposed an approach for integrating GS for quantitative traits within the most promising offspring. In this approach, seedlings of each of the best hybrid progeny are grown in the greenhouse, and in the following year planting as TP a sample of them in replicated small field plots (e.g., 10 plants) for assessing traits in the target environment to avoid genotype × environment interactions. The remaining breeding clones (BP) will undergo GS, thus reducing the time and costs of field testing for selecting parents for the next cycle crossing cycle or identifying promising bred germplasm for potential cultivar releases.

Table 2. Summary of recent research findings on genomic prediction of breeding values in potato.

Trait	Main Output(s) in Reference Population	References
Host plant resistance to late blight	Prediction accuracy ca. 0.8, irrespective of model, for maturity corrected resistance in tetraploid German breeding clones	[100]
	Genomic heritability of 0.46 ± 0.04 with estimated prediction correlation of ca. 0.31 in advanced US tetraploid breeding clones	[102]
Host plant resistance to common scab	Genomic heritability of 0.45 ± 0.02 with estimated prediction correlation of ca. 0.27–0.31 in advanced US tetraploid breeding clones	[102]
Tuber flesh color	Prediction accuracy (after cross validation) above or equal to 0.7 except when using Bayes C (0.59) in European cultivars	[101]
Starch content	Cross-prediction validation correlation of 0.56 in training panel but between 0.30 and 0.31 in test panel derived from tetraploid mapping population of breeding program in Denmark	[99]
	Prediction accuracy increasing by 8% if model includes additive and dominance effects rather than only additive effects in tetraploid German breeding clones	[100]
Tuber dry matter or specific gravity	SNPs captured 20% of additive genetic variance of the total genetic variance; prediction accuracy ranging between 0.25 and 0.63 in unselected US F_1 tetraploid breeding population	[96]
	Cross-prediction validation correlations ranged from 0.75 to 0.83 when combining tetraploid mapping populations of breeding program in Denmark but ranging between 0.37 and 0.71 when predicting across populations	[98]
	Average prediction accuracy (cross-validation) across models of 0.65 (0.54–0.68) in European cultivars	[101]
Frying chipping quality	SNPs captured 45% of additive genetic variance of the total genetic variance; prediction accuracy ranging between 0.4 and 0.45 when using different pedigree depth in unselected US F_1 tetraploid breeding population	[96]
	Cross-prediction validation correlations ranged from 0.39 to 0.79 when combining tetraploid mapping populations of breeding program in Denmark but ranging between 0.28 and 0.48 when predicting across populations	[98]
	Cross-prediction validation correlation of 0.73 in training panel but between 0.42 and 0.43 in test panel from tetraploid mapping population of breeding program in Denmark	[99]
Stem number per plant	Average prediction accuracy (cross-validation) across models of 0.05 (0.01–0.13) in European cultivars	[101]

Table 2. *Cont*.

Trait	Main Output(s) in Reference Population	References
Tuber yield and components	SNPs captured 45% of additive genetic variance of the total genetic variance; prediction accuracy ranging between 0.06 and 0.63 in unselected US F_1 tetraploid breeding population	[96]
	8% increase in prediction model accuracy when using both additive and dominance effects instead of additive effects only in tetraploid German breeding clones	[100]
	Average prediction accuracy (cross-validation) across models of 0.37 (0.22–0.41), 0.32 (0.15–0.41), and 0.17 (0.13–0.23) for total yield, size (as measured by diameter) and number, respectively, in European cultivars	[101]

OUTLOOK: REWRITING THE POTATO BREEDER'S EQUATION

Potato breeding has been using mostly a phenotypic recurrent selection approach across generations and selecting therein promising clones for further cultivar releases. Slater et al. [105] noticed that marker-aided selection (MAS) appears to be cost-effective, particularly for quantitative traits. Furthermore, they indicated that using MAS along with estimated breeding values may reduce the breeding cycle from 10 to 4 years, while GS will bring it down to 1 year (by selecting early and intensely in the first seedling generation rather than waiting for field testing), thus accelerating genetic gains significantly. Likewise, high throughput phenotyping (HTP) with imaging sensors in greenhouses and unmanned aerial vehicles with sensors for field phenotyping will both reduce cost-effectively the breeding cycle and offer means for breeding potatoes differently. Large-scale phenotyping will also improve GS accuracy. For example, infrared thermography provides an easy, fast and non-destructive method for tuber yield when potatoes are grown under plentiful moisture [106], while near-infrared reflection spectroscopy may be used for predicting crude protein and dry matter contents in potato tubers [107].

Although, as reiterated recently [108], DNA markers linked to target traits assists potato germplasm enhancement while introgressing genes or incorporating genetic resources from crop wild relatives or landraces, speeding up gains by reducing the breeding cycle remains a key goal. In this regard, producing potatoes from true seed-propagated F_1 diploid hybrids after crossing inbred diploid lines are being pursued both in Europe [109] and North America [110], and its great potential already shown in East Africa [111]. This breeding approach brings a new step in the evolution of potato breeding; i.e., crop re-domestication by returning to diploidy for implementing an inbred line strategy that reduces genetic load through inbreeding and thereafter combines target traits through hybridization [112]. Marker-aided backcrossing may be further used for introducing desired genes from other potato germplasm (e.g., host plant resistance or tuber quality) into elite diploid inbred lines. However, a

gametophytic self-incompatibility system makes difficult developing inbred lines in diploid potatoes. Nonetheless, the use of the dominant *S-locus inhibitor* (*Sli*) allele—found in *S. chacoense*—beats this hurdle [113]. Moreover, gene editing using CRISPR/Cas 9 has been shown to knock out the self-incompatibility gene *S-RNase*, thus facilitating inbreeding in diploid potato [114]. Likewise, some haploids derived from tetraploid potatoes may be both self-compatible and male fertile, thus allowing selfing. It is worth noting that recessive allele frequency changes owing to selection may be faster at the diploid than at the tetraploid level because the recessive allele is only hidden by the heterozygous in the diploids whereas simplex, duplex and triplex include it in the tetraploids. In theory, sq^2 individuals having a recessive genotype will be selected in a large diploid breeding population with q being the allele frequency and s the intensity of selection, while sq^4 denotes the fraction of recessive genotypes selected in a large tetraploid breeding population. Hence, diploid improvement offers new routes to accelerate and increase genetic gains in potato breeding because overcomes inherent barriers due to ploidy, outcrossing and heterozygosity of this crop [115]. Furthermore, F_1 true-seed propagated hybrids will avoid accumulating pathogens in and physiological decline of potato tubers, which have also a high storage and transport costs.

Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein-9 (CRISPR-Cas9) offers means for gene editing in potato, as shown elsewhere [116]. Gene editing using tetraploid potato protoplast may lead to mutations in the four alleles in a single transfection [117]. Desired traits to pursue are, *inter alia*, related to starch quality, reduced glycoalkaloids, regulating enzymatic darkening process, resisting blackspot bruising, having less asparagine that change into acrylamide after frying, or host plant resistance to pathogens and pests. Gene editing can also used for targeted improvement through promoting alleles in a potato breeding population, thus accelerating and increasing genetic gains (Δ_G)—which lead to rewriting its equation as follows:

$$\Delta_G = \frac{a\, i\, \sigma^2}{t} + \text{gene editing for promoting desired alleles} \quad (1)$$

where a, i, σ^2 and t are accuracy that may improve due to HTP, selection intensity by increasing the effective population size using early testing coupled with GS, genetic variation for target trait(s) that may be enhanced by incorporating useful exotic germplasm, and time spent in each cycle through speed breeding, respectively. Combining marker-aided selection and estimating breeding values may further improve potato breeding efficiency by significantly reducing the cycle length to identify promising germplasm.

Considering the genetic enhancement research advances and new breeding techniques or tools as described in previous paragraphs, a new approach for population improvement and cultivar development may be envisaged (Figure 1). In this approach, (maternal) haploids are extracted

from elite tetraploid breeding cultivars, and thereafter included in crossing blocks with exotic (crop wild relatives or landrace) diploid germplasm for base broadening or introgression of desired gene(s). Further diploid or tetraploid genomic recurrent selection within each defined heterotic group leads to diverse and improved breeding populations at each ploidy level. Although ploidy manipulations offer means for introgressing and incorporating genetic resources from wild relatives in potato breeding, obtaining large segregating tetraploid populations through sexual polyploidization with 2*n* gametes often remains as a challenge. Such a limitation must be overcome as well as pursuing "nobilization" through backcrossing to the cultigen pool to eliminate most of the linkage drag from the wild species genome. Interpopulation genomic reciprocal recurrent selection allows diploid inbred line development for further crossing and producing F_1 hybrids. Likewise, crossing blocks considering heterotic groups and estimated breeding values result in tetraploid hybrid seed that is used for clonal breeding in cultivar development. Gene editing in the elite bred germplasm may be pursued for promoting alleles controlling desired traits and missing in the breeding populations.

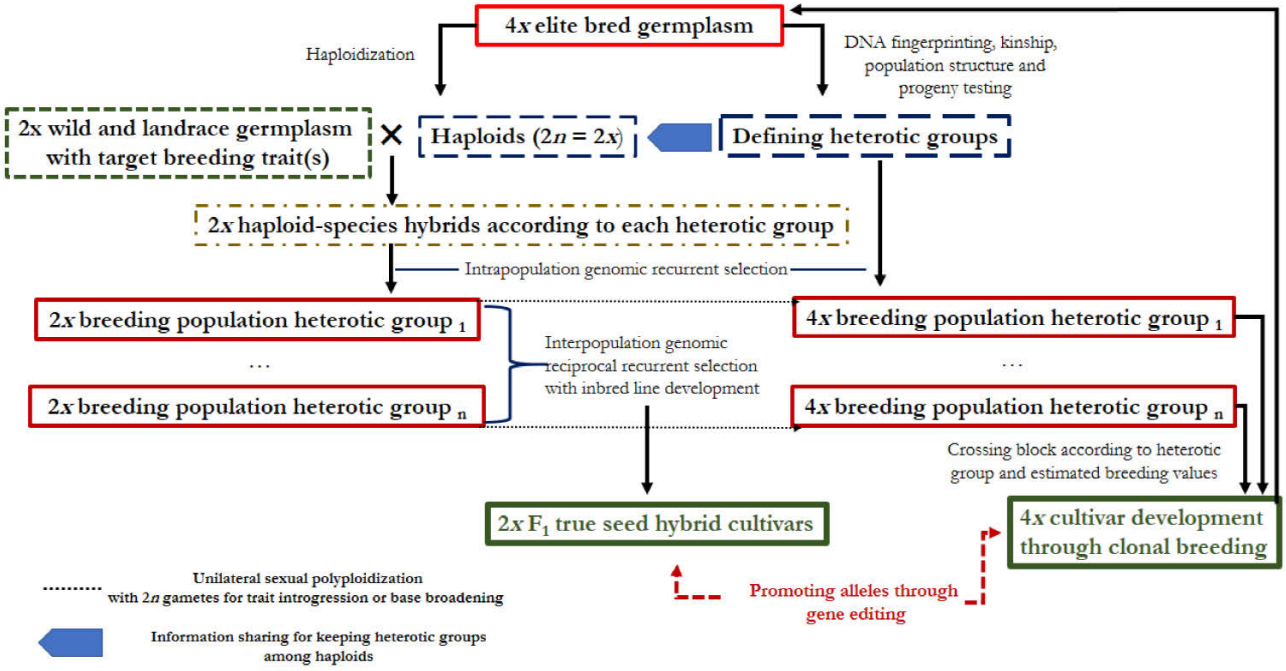

Figure 1. Diagram showing an interploidy breeding approach for population improvement and cultivar development in potato.

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