Statistical epistasis between candidate gene alleles for complex tuber traits in an association mapping population of tetraploid potato

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Abstract Association mapping using DNA-based markers is a novel tool in plant genetics for the analysis of complex traits. Potato tuber yield, starch content, starch yield and chip color are complex traits of agronomic relevance, for which carbohydrate metabolism plays an important role. At the functional level, the genes and biochemical pathways involved in carbohydrate metabolism are among the best studied in plants. Quantitative traits such as tuber starch and sugar content are therefore models for association genetics in potato based on candidate genes. In an association mapping experiment conducted with a population of 243 tetraploid potato varieties and breeding clones, we previously identified associations between individual candidate gene alleles and tuber starch content, starch yield and chip quality. In the present paper, we tested 190 DNA markers at 36 loci scored in the same association mapping population for pairwise statistical epistatic interactions. Fifty marker pairs were associated mainly with tuber starch content and/or starch yield, at a cut-off value of \( q \leq 0.20 \) for the experiment-wide false discovery rate (FDR). Thirteen marker pairs had an FDR of \( q \leq 0.10 \). Alleles at loci encoding ribulose-bisphosphate carboxylase/oxygenase activase (Rca), sucrose phosphate synthase (Sps) and vacuolar invertase (Pain1) were most frequently involved in statistical epistatic interactions. The largest effect on tuber starch content and starch yield was observed for the paired alleles Pain1-8c and Rca-1a, explaining 9 and 10% of the total variance, respectively. The combination of these two alleles increased the means of tuber starch content and starch yield. Biological models to explain the observed statistical epistatic interactions are discussed.

Introduction

Association or linkage disequilibrium mapping using DNA-based markers is a novel tool in plant genetics for the analysis of complex traits (Gupta et al. 2005; Holland 2007). In association mapping studies, phenotypes and genotypes are evaluated in populations of individuals descending from multiple crosses between different parents rather than in progeny of controlled crosses between two parental genotypes. In the latter, the genotypic and phenotypic variations present in the two parents are analyzed, whereas the former captures the genotypic and phenotypic variations of many individuals (Mackay and Powell 2007). Association genetics is particularly useful in cultivated potato (Solanum tuberosum), a tetraploid, non-inbred crop species, where linkage analysis in experimental, tetraploid populations is complicated by tetrasomic inheritance (Luo et al. 2001). Moreover, potato breeding is based on inter-crossing multiple, heterozygous parents followed by multi-year selection in the segregating first filial generation. The
In a previous study, we identified DNA variation in genes that function in carbohydrate metabolism or transport, which was tested for association with tuber yield, starch content, starch yield and chip color in a population of tetraploid varieties and breeding clones derived from advanced potato breeding programs. Highly significant and robust associations between individual candidate gene alleles and the traits were discovered (Li et al. 2008). In this paper, we report on the results of analyzing the genotypic and phenotypic data of this association mapping experiment for two-way epistatic interactions.

Materials and methods

Plant material

The analysis of two-way epistatic interactions was based on the phenotypic and genotypic data of 243 tetraploid individuals, which included 34 varieties as standards and 90, 96 and 23 clones from the breeding programs for chips, starch and table potatoes of the companies Böhm-Nordkartoffel Agrarproduktion (BNA), SAKA Pflanzenzucht (SAR) and NORIKA (NOR), respectively. Further details of this population referred to as population ‘ALL’ are described elsewhere (Li et al. 2008).

Phenotypic data

Tubers of the individuals of the ALL population were evaluated in 2 years as described (Li et al. 2008) for starch content (TSC, percent fresh weight), yield (TY, dt/ha = deciton per hectare, 1 dt = 100 kg), starch yield (TSY = TSC × TY, dt/ha), chip quality after harvest (CQA, score between 1 and 9, 1 = very bad chip quality; 9 = very good chip quality) and after 3–4 months storage at 4°C (CQS). Tuber starch content was determined by measuring specific gravity. Tuber yield was determined by the tuber weight. Tuber starch yield is the product of TSC and TY. Chip quality was assessed by visually scoring the chip color after deep frying of 1.2–2.0 mm tuber slices in oil at 160–180°C for 2–3 min.

Genotypic data

Genotyping of the population ALL has been described (Li et al. 2008). In brief, 36 loci on all potato chromosomes except chromosome I were evaluated for the presence or absence of 190 single strand conformation polymorphism (SSCP), simple sequence repeat (SSR), cleaved amplified polymorphic sequence (CAPS), sequence characterized amplified region (SCAR) and allele specific amplification (ASA) DNA fragments. Twenty-two loci encoded genes...
related to carbohydrate metabolism or transport. The remaining loci were anonymous markers such as SSRs. All DNA fragments were scored as present (1) or absent (0) in each individual, with some missing values.

Statistical analysis

As a preliminary to the association analysis, population substructure was evaluated using the software STRUCTURE (Pritchard et al. 2000) as described (Li et al. 2008). For an assumed number of groups K between 1 and 30 we found that the likelihood increased steadily with increasing K, and we found no evidence of population structure for the present set of genotypes. We also explored the genetic relationships with the first two principal components, which accounted for more than 40% of the total genetic variation, and these components represented a grouping similar to the origin of the genotypes. Therefore, we included the factor ‘origin’ in our association analyses. Origin had four levels corresponding to the genotype groups “SAR”, “BNA” and “NOR” and the group “Standards”.

Analysis of epistatic interactions was thus performed using the regression model:

\[ y^* = \text{origin} + \text{marker}_i + \text{marker}_j + \text{marker}_i \times \text{marker}_j + \text{error} \]

where \( y^* \) stands for adjusted trait means as described (Li et al. 2008). Factors \( \text{marker}_i \) and \( \text{marker}_j \) had two levels, indicating whether a DNA fragment was present or absent. The epistatic effect between the two markers \( \text{marker}_i \) and \( \text{marker}_j \) was tested by a partial t test, after correcting for origin and the additive main effects of the two markers. We tested epistasis between all possible marker pairs. The proportion of genetic variation explained by an epistatic interaction was calculated as the relative increase in \( R^2 \) after the interaction effect is added to the model including origin and marker main effects.

Correction for multiple testing:

We included a correction for multiple testing aiming at the false discovery rate (FDR) (Storey and Tibshirani 2003): the proportion of false positives in the set of epistatic interactions for which the null hypothesis of no interaction is rejected. The \( P \) values resulting from testing epistasis in our regression model were converted into so-called \( q \) values that estimate FDR, according to the method of Allison et al. (2002), available in Genstat’s procedure FDRMIXTURE [GenStat (2005) GenStat 8rd edn. Release 8.1. VSN International Ltd., Oxford, UK]. In this approach, the \( P \) values are assumed to come from a mixture of two distributions, a uniform density corresponding to \( P \) values obtained from \( H_0 \) tests, and a Beta density for \( P \) values obtained from \( H_1 \) tests. The method estimates the proportion of true \( H_0 \) tests and the parameters of the Beta density, and \( q \) values are produced according to the fitted parameters. Here, we report epistatic interactions with an FDR of \( q \leq 0.20 \).

**Results**

Pairwise tests for epistatic interactions between 190 polymorphic DNA fragments derived from 36 loci resulted in 17,956 tests each for tuber starch content (TSC), tuber yield (TY), tuber starch yield (TSY), chip quality after harvest (CQA) and after cold storage (CQS). Experiment-wide FDRs (\( q \) values) were calculated by applying the multiple testing correction described in “Materials and methods”. The number of interaction pairs with \( 0.20 < q \leq 0.30 \), \( 0.10 < q \leq 0.20 \) and \( q \leq 0.10 \) is shown in Fig. 1. When choosing as cut-off value \( q < 0.20 \), no interaction pair remained for tuber yield and only few interaction pairs remained for chip quality. The majority of interaction pairs was found for tuber starch content and starch yield (Fig. 1). Interaction pairs for TSC and TSY partially overlapped (the same marker pair

![Fig. 1](image-url)
showed interaction for TSC and TSY) and some were redundant. Redundant interaction pairs resulted from different DNA fragments amplified from different regions of the same gene that were in very high or absolute linkage disequilibrium with each other and showed therefore similar interactions (Li et al. 2008). When redundant interaction pairs were removed from the data set, 50 marker pairs remained (Table 1; Supplementary Table 1), 13 of which were significant at \( q \leq 0.10 \) for either TSC or TSY or both (Table 2). These 13 interaction pairs explained between 5 and 10% of the total variance (Table 2). Eight of the 20 different alleles forming the 13 interaction pairs had also shown main effects for at least one of the traits CQA, CQS, TSC, TSY and TY (Li et al. 2008). The most significant interaction (\( q < 0.05 \)) for both TSC and TSY involved the alleles \( Rca-1a \) and \( Pain1-8c \) at two loci encoding ribulose-bisphosphate carboxylase and soluble acid invertase, respectively (Table 2). Mean and standard errors for TSC and TSY of the four marker genotype classes of the 13 most significant marker pairs in are shown in Table 3. The 13 most significant interaction pairs involved 15 loci (Table 2), whereas the 50 interaction pairs involved 31 of the 36 loci genotyped in the ALL population (supplementary Table 1; Fig. 2). Alleles at the loci \( Sps \) (sucrose phosphate synthase), \( Rca \) (ribulose-bisphosphate carboxylase activase) and \( Pain1 \) (soluble acid invertase) on chromosomes VII, X and III, respectively, were most frequently participating in interactions (Fig. 2). The \( Sps \) alleles 7c, 7d and 7e were partner in 13 interactions, the \( Pain1 \) alleles 8c/9a (8c and 9a are in strong LD with each other), 5b and 5d were partner in 8 interactions and the \( Rca \) alleles 1a and 3b were partner in 11 interactions. Thirty of the 50 interaction pairs involved at least one allele of these three loci (Table 2; Supplementary Table 1).

### Discussion

When searching for statistical epistatic interactions, the problem of false positives due to multiple testing is aggravated. At the same time, the power of the two-way test statistic is reduced compared with single marker association tests. A too stringent multiple testing correction might obscure true interactions, whereas no correction inflates the number of false positives. In this paper we report epistatic interactions with an experiment-wide FDR of 20% (\( q \leq 0.20 \)) (Kraakman et al. 2004). With this threshold, 50 marker pairs were associated with at least one of the five quantitative traits. Twenty percent or around ten of those pairs are expected to be false positives. With the more stringent threshold of 10% FDR (\( q \leq 0.10 \)) 13 marker pairs remained, one or two of which are expected to be false positives.

### Table 1

Number of pairwise epistatic interactions at \( q \leq 0.20 \)

| Traits | Number of interaction pairs |
|--------|-----------------------------|
| TSC    | 13                          |
| TSY    | 17                          |
| TSC and TSY | 16                      |
| CQA    | 3                           |
| TSC, TSY and CQS | 1                      |

\[ \Sigma = 50 \]

### Table 2

Pairwise epistatic interactions significant at \( q \leq 0.10 \) for TSC and/or TSY

| Locus 1 | Chromosome number | Locus 2 | Chromosome number | Allele 1 | Allele 2 | TSC | \( R^2 \) (%) | TSY | \( R^2 \) (%) |
|---------|------------------|---------|------------------|----------|----------|-----|----------------|-----|----------------|
| Pain1   | III              | Rca     | X                | Pain1-8c | Rca-1a   | 0.0336 | 9.13         | 0.0185 | 10.27         |
| Pain1   | III              | Rca     | X                | Pain1-5d | Rca-1a   | 0.0745 | 6.74         | 0.0977 | 5.81          |
| STM3012 | IX               | Rca     | X                | STM3012-a | Rca-1a   | 0.0608 | 7.23         | 0.1188 | 5.53          |
| STM3012 | IX               | Rca     | X                | STM3012-b | Rca-1a   | 0.0888 | 6.57         | 0.1065 | 5.84          |
| STM1106 | X                | Rca     | X                | STM1106-m | Rca-1a   | 0.0947 | 6.58         | 0.1130 | 5.72          |
| STM1106 | X                | Rca     | X                | STM1106-f | Rca-1a   | 0.1832 | 5.15         | 0.0472 | 7.25          |
| Satl    | XI               | Rca     | X                | Satl-7b  | Rca-1a   | 0.0817 | 7.07         | 0.1855 | 4.86          |
| STM1052 | IX               | Inv-ap-b | IX          | STM1052-a | InvGE-6i | 0.0611 | 7.60         | >0.3   | 2.72          |
| G6pdh   | II               | Inv-ap-b | IX          | G6pdh-4b | InvGF-4d | 0.1834 | 5.13         | 0.0575 | 6.81          |
| AGPaseB-a | VII            | Sps     | VII             | AGPaseb-6a | Sps-7e | 0.0730 | 7.55         | 0.0794 | 6.59          |
| GP171   | VIII             | Sps     | VII             | GP171-a | Sps-7e | 0.1000 | 6.01         | 0.0639 | 6.44          |
| Stl 1.1 | XI               | Sus4    | XII             | Stl1.1-Hinfl | Sus4-2c | 0.0878 | 6.47         | >0.3   | 2.89          |
| Sssl    | III              | Dbe     | XI              | Sssl-7a | Dbe-5c | 0.2744 | 4.08         | 0.1063 | 5.66          |

\(^a\) The same marker allele showed a significant (\( q \leq 0.05 \)) main effect on at least one of the traits CQA, CQS, TSC, TSY and TY (Li et al. 2008)
Table 3 Number of individuals, phenotypic mean and standard errors (SE) of marker genotype classes 11 (both alleles present), 00 (both alleles absent), 10 (allele 1 present, allele 2 absent) and 01 (allele 1 absent, allele 2 present) for epistatic interactions with $q \leq 0.10$

| Allele 1 | Allele 2 | No. of individuals per genotype class | TSC genotype class mean (SE) (%) | TSY genotype class mean (SE) (dt/ha) |
|----------|----------|--------------------------------------|---------------------------------|-------------------------------------|
| 11       | 00       | 10                                  | 01                              | 11                                 |
| Pain1-8c | Rca-1a   | 14 93 32 57                          | 21.4 (0.8) 17.1 (0.4) 18.1 (0.5) 15.4 (0.5) | 138.5 (6.0) 104.4 (2.6) 107.8 (3.7) 96.6 (3.3) |
| Pain1-5d | Rca-1a   | 9 145 16 69                          | 21.1 (1.0) 17.3 (0.3) 16.8 (0.8) 15.9 (0.4) | 134.9 (7.3) 104.8 (2.0) 99.7 (5.5) 100.4 (3.0) |
| STM8912-a| Rca-1a   | 46 63 96 34                          | 15.3 (0.5) 16.9 (0.4) 17.3 (0.3) 18.5 (0.6) | 96.4 (3.5) 101.4 (2.8) 105.3 (2.4) 116.2 (4.1) |
| STM8912-b| Rca-1a   | 22 122 32 57                         | 19.3 (0.7) 17.2 (0.3) 16.9 (0.5) 15.7 (0.4) | 122.6 (4.9) 104.1 (2.2) 100.4 (3.8) 98.7 (3.2) |
| STM1106-m| Rca-1a   | 4 150 7 72                           | 22.4 (1.5) 17.3 (0.3) 15.8 (1.1) 16.2 (0.4) | 145.3 (10.7) 104.6 (1.9) 94.3 (8.0) 101.6 (2.9) |
| STM1106-f| Rca-1a   | 7 144 13 69                          | 20.7 (1.1) 17.2 (0.3) 16.6 (0.8) 16.1 (0.4) | 137.8 (8.1) 104.6 (1.9) 95.7 (5.9) 137.8 (2.9) |
| Sts1-7b  | Rca-1a   | 58 52 100 17                         | 16.0 (0.4) 16.7 (0.4) 19.4 (0.7) 17.3 (0.3) | 100.3 (3.2) 102.7 (3.0) 123.8 (5.4) 104.5 (2.4) |
| STM1052-a| InvGE-6i  | 118 64 17 31                         | 16.8 (0.3) 16.5 (0.4) 18.9 (0.7) 18.6 (0.9) | ns a ns ns ns |
| G6pdh-4b | InvGF-4d  | 23 93 73 51                          | 15.1 (0.6) 16.8 (0.4) 17.4 (0.4) 17.7 (0.5) | 89.9 (4.5) 99.6 (2.5) 110.6 (2.5) 106.8 (3.2) |
| AGPsb-6a | Sps-7c    | 76 51 38 61                          | 16.1 (0.3) 15.4 (0.7) 18.1 (0.3) 17.6 (0.7) | 101.4 (2.6) 98.5 (2.9) 108.2 (3.4) 115.6 (2.9) |
| GP171-a  | Sps-7e    | 97 20 18 107                         | 16.6 (0.3) 15.1 (0.5) 17.7 (0.3) 17.7 (0.5) | 97.7 (2.4) 92.9 (5.0) 109.8 (2.2) 114.0 (2.4) |
| Sts1-1-Hinf | Sst4-2a   | 81 38 89 34                          | ns ns ns ns                          | 100.0 (2.5) 93.0 (3.8) 116.1 (2.6) 100.9 (3.2) |
| Sst1-7a  | Dbe-5c    | 76 31 70 48                          | ns ns ns ns                          | ns ns ns ns |

*Not significant with the threshold $q \leq 0.20$
The choice of candidate loci based on their function in carbohydrate metabolism and transport was more suitable to detect associations with chip quality, tuber starch content and starch yield than with tuber yield.

As a good set of functional candidate genes for yield is not available, whole genome association mapping is more appropriate to dissect tuber yield.

Three loci, Sps, Pain1 and Rca, were exceptional with respect to the number of epistatic interactions they showed with each other and with other loci. The genes encoded at these loci may be either directly causal for the observed effects, or the associations are indirect due to linkage disequilibrium with the causal genes that are physically linked but different. Linkage disequilibrium in potato can extend over few Centimorgans in the genetic material used here for association mapping (Li et al. 2008). Nevertheless, the central functional roles of Rca, Sps and Pain1 in carbon fixation and partitioning into sugars and starch suggest a possible explanation for the observed frequency of epistatic interactions. Photosynthetic CO2 fixation in chloroplasts is catalyzed by ribulose 1,5-bisphosphate carboxylase/oxygenase (Rubisco). The activity of Rubisco is regulated by Rubisco activase (RCA) (Mate et al. 1993; Portis 1990; Salvucci and Ogren 1996). Fixed carbon is transitory deposited in chloroplasts as starch and after starch degradation transported as triose-phosphate into the cytoplasm of leaf mesophyll cells, where it is partitioned in sugars, other metabolites and respiratory pathways. Cytoplasmic sucrose phosphate synthase (SPS) has a key role in the synthesis of sucrose (Huber and Huber 1992; Stitt et al.
1988; Winter et al. 2000), the metabolite by which carbon is mainly exported from the leaves and transported through the vascular system to the developing tuber, where it is stored as starch in the amyloplasts of parenchyma cells (Frommer and Sonnewald 1995). Several invertase isoforms are present in source as well as sink tissues and cleave sucrose irreversibly in glucose and fructose in different cellular compartments, the apoplastic space, the cytoplasm and the vacuole. By controlling the ratio of sucrose to hexoses, invertases are crucial for the strength of metabolic sinks such as tubers, for growth and for carbon partitioning. High sucrose-to-hexose ratios favor the channeling of carbon into storage compounds whereas low sucrose-to-hexose ratios promote cell division and growth (Sturm and Tang 1999; Tymowska-Lalanne et al. 1998; Winter et al. 2000). The Pain1 locus encodes a vacuolar invertase, which together with apoplastic invertases controls the ratio of sucrose to hexose in tubers (Zrenner et al. 1996). Thus, the Sps, Pain1 and Rca loci are linked with each other and with many other enzymes through the metabolic flux from photosynthetic (source) to storage (sink) organs. Natural allelic DNA variation in the coding and/or non-coding regions of a gene can cause non-destructive functional modification of the gene product, by modulating its expression, translation, posttranslational modification, transport, degradation and/or catalytic properties. When connected with many other proteins in a metabolic network, the effect of allelic variation at one locus is likely to depend on the allelic variation at a second and more loci (Alcazar et al. 2009). Higher order interactions were not tested in the present data set.

Interestingly, the most significant epistatic interaction was observed between the alleles Rca-1a and Pain1-8c (q < 0.05). This interaction explained 9 and 10% of the total variance of TSC and TSY, respectively. When tested individually, both alleles were associated with tuber quality traits. The Rca-1a allele decreased, on average, chip quality (CQA and CQS), whereas the Pain1-8c allele increased, on average, CQA, CQS, TSC and TSY (Li et al. 2008). The combination of both alleles had no effect on chip quality any more but increased tuber starch content by 3–5% and starch yield by 20–40 dt/ha, compared with the other three allele combinations (Table 3). The following model is compatible with these observed effects: The Rca-1a allele activates Rubisco more compared to other Rca alleles, which leads to a higher rate of CO2 fixation in plants carrying this allele. On the other hand, the Pain1-8c allele encodes an invertase that is less effective than other invertase alleles in sucrose cleavage, thereby shifting the balance towards higher sucrose-to-hexose ratios in carrier plants. The combination of a more active Rca allele with a less effective invertase allele partitions more carbon into starch and increases tuber starch content and starch yield. In contrast, the combination of a more active Rca allele with ‘normal’ invertase alleles leads to lower sucrose-to-hexose ratios, higher contents of glucose and fructose, thereby decreasing chip quality, which is inversely correlated with glucose and fructose content. Vice versa, a less effective invertase allele in combination with ‘normal’ Rca alleles can still have positive effects on chip quality, tuber starch content and starch yield. The allele dosage might be an important factor in interaction models in polyploid species. However, the allele dosage could not be scored when using SSCP for detection of DNA polymorphisms. More research is needed to verify this model and to elucidate the mechanisms that determine the quality of natural alleles in the context of metabolic networks.

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