

Supplementary Figure 1. Mutant and WT D2HGDH are co-expressed in DLBCL. Sequencing tracing of RT-PCR products representing the expression levels of three DLCBL-associated D2HGDH mutations indicate that the mutant and WT alleles are equally expressed. The frame-shift nature of the G131X prevented a clear display of the histogram for that variant. However, cloning and sequencing of those RT-PCR products showed a balanced representation of WT and mutant forms (4 mutant, 6 WT in 10 clones – data not shown). No mRNA was available from tumours harbouring the R212W mutation. The expression of A426T mutation is shown in both a cell line and in a primary DLBCL.



Supplementary Figure 2. D2HGDH is a self-interacting protein. a) FLAG- or HA-tagged D2HGDH WT and mutant constructs were co-transfected in HEK-293 cells (different combinations of WT and mutant proteins are listed on the top). Immunoprecipation (IP) of D2HGDH-FLAG pulled-down HA-D2HGDH (left panel - top). Likewise, IP of HA-D2HGDH, brought-down D2HGDH-FLAG (middle panel - top). These data indicate that D2HGDH selfcomplexes and that the DLBCL-associated mutations do not disrupt this binding. Note that the G131X truncating mutation probably results in an unstable protein (predicted size 17KD), which could not be detected with N-terminus tagging (HA-D2HGDH-G131X – see input blot). The HA-IP/IB yields a non-specific band indicated by an *. Cotransfection of empty-vectors, re-probing with FLAG or HA antibodies, and IP with control IgG (middle and lower panels, respectively) confirmed the specificity of these assays. Input protein is shown on the far right panel. b). The D2HGDH self-association was further confirmed by analysing the proteins in denaturing vs. non-denaturing conditions. Again, FLAG- or HA-tagged D2HGDH WT and mutant constructs were co-transfected in HEK-293 cells (the different combinations of WT and mutant proteins are listed on the top). On the left, using three different antibodies and denaturing conditions D2HGDH expression is readily identified at its predicted size. On the right panels, non-denaturing gels revealed a larger product (indicated by brackets) detected every time D2HGDH is ectopically expressed (note its absence in the HA-G131X expressing cells, when IB with HA, and in all instances of empty HA and FLAG vectors co-expression). The D2HGDH self-interacting complex was detected between two D2HGDH-WT molecules (2nd lane from the left), as well as between D2HGDH-WT and any of the four missense D2HGDH mutants (A208T, R212W, R421H, A426T). At the moment we can not exclude the possibility that the selfassembly of D2HGDH includes more than two molecules. (i.e., homotrimer, homotetramer, etc.) or that other proteins are part of this complex (heterotrimer, etc.). *, non-specific band. Red arrow – D2HGDH at its predicted size.



Supplementary Figure 3. D2HGDH mitochondrial localization by immunofluorescence. HEK-293 cells stably expressing WT or each D2HGDH mutant were co-stained with the mitochondrial probe MitoTracker (green), and with an anti-D2HGDH antibody (Cy3, red). D2HGDH-expressing cells are also GFP positive (pseudocolored in blue). Merged images indicate that, as expected, WT D2HGDH localizes to the mitochondria, and that the mutations analysed do not change this subcellular localization. As the D2HGDH antibody targets a C-terminus epitope, the truncated G131X mutant is not recognized and thus its subcellular distribution cannot be determined. Cells were imaged on an Olympus FV1000 confocal microscope, at 60x magnification (scale bar is 10µm).



Supplementary Figure 4. HPLC-ESI-MS-based quantification of D2-HG and α-KG. Metabolites were extracted from HEK-293 cells stably expressing WT or mutant D2HGDH constructs. In a) and b) we show that expression of WT D2HGDH led to a decrease in D2-HG when compared to cells expressing the G131X, R208T, and R212W mutants (but not R421H or A426T) (in a, p<0.0001, in b, p=0.0002, ANOVA; in both p<0.05 Bonferroni's Multiple Comparison post-test). Data in a and b represent two biologically independent assays, performed with five and three replicates/sample type, respectively. In c), we show that expression of D2HGDH (WT or mutant) does not alter the levels of L2-HG - assay performed with three replicates/sample type. In d), e) and f), we show that expression of D2HGDH-WT result in a significant accumulation of α -KG when compared to cells expressing an empty or any of the DLBCL-associated mutants (in c and d, p< 0.0001, in e p=0.0112, ANOVA; in all three assays p<0.05 Bonferroni's Multiple Comparison post-test). Data in d, e and f, represent three biologically independent assays, performed with four or five replicates/sample type. The data from panel a) and d) are shown in Figure 1a, depicting the relative abundance of D2-HG and α-KG in models of stable D2HGDH expression. Western blot (bottom) confirms the similar expression of WT and mutant D2HGDH - the antibody used is directed to the C-terminus region and would not detect the G131X truncated protein, which is likely to be unstable (see supplementary Figure 3). Metabolites quantifications were normalized by protein amount (mg).



Supplementary Figure 5. D2HGDH expression levels in the transient transfection model are within endogenous expression range. Western blot analysis of D2HGDH in HEK-293 cells transiently transfected with an empty vector (MSCV, 1µg), or increasing amounts of a MSCV-D2HGDH construct (0.5µg, 0.75 µg and 1.0 µg) alongside a subset of the B cell lymphoma cell lines used in this study. This assay demonstrated that the expression level achieved in the transient transfection assay is within the range of endogenous D2HGDH expression found in B lymphoma cell lines. Densitometric quantification, normalized by β -actin, is show at the bottom.



Supplementary Figure 6. HPLC-ESI-MS-based quantification of D2-HG and α -KG in cells transiently expressing wild-type D2HGDH. Metabolites were extracted from HEK-293 transiently expressing an empty vector or a WT D2HGDH construct. a) and b) represent two independent transient transfection assays, and in each instance the left panel depicts D2-HG level and the right panel, α -KG. Western blot examination confirmed the subtle increase in D2HGDH expression in this model, which resulted in a progressive, significant, decrease in D2-HG levels (left panels in a) and b), p=0.0002 and p=0.0003, respectively – ANOVA). Concordantly, increasing D2HGDH expression significantly elevated the levels of α -KG in these cells (right panels, in a) and b), p=0.0068 and p<0.0001, respectively – ANOVA). All data shown represent mean and SD of three replicates/sample type. The data from panel a) are shown in Figure 1d, which depicts the relative abundance of D2-HG and α -KG. Densitometric quantification, normalized by β -actin, is show at the bottom of the western blots.



Supplementary Figure 7. Differential effects of WT and mutant D2HGDH towards α -KG-dependent dioxygenases a) Histone demethylases: the methylation of H3 lysine residues was determined by western blot in HEK-293 stably expressing WT or mutant D2HGDH; whereas the WT enzyme suppressed K4, K9, K27 methylation, expression of the mutant proteins had little or no effect, and mimicked the empty MSCV control cells. Note that the H3K79me2 level is not influenced by D2HGDH, as this lysine is not regulated by the Jumonji family of α-KGdependent demethylases. Densitometric quantification, normalized by β-actin, is show at the bottom of each panel. b) HIF1 α prolyl-hydroxylases: under hypoxia (1% O₂, 16h), the levels of HIF1 α hydroxylation (Pro-402) were increased and total HIF1α markedly decreased in cells expressing WT but not any of the mutant D2HGDH enzymes. c) TET enzymes: Top panel: The levels of 5hmC were quantified by intracellular FACS and found to be lower in cells expressing mutant D2HGDH than in WT cells, as shown by the left-shift of D2HGDH-mutant expressing cells in the histogram. Mid panel: The quantification of 5hmC marks was also performed using a capture and detection antibodybased approach. Abundance of 5hmC marks was measured by absorbance, and reported as relative values normalized by a positive control, a polynucleotide containing 20% 5hmC. Cells expressing empty vector (MSCV) or any of the D2HGDH mutant enzymes had significantly lower levels of 5hmC- modified DNA than the D2HGDH WT cells (p<0.001, one-way ANOVA, p<0.05, Bonferroni's multiple comparison post-test). These data represent the mean and SD of an assay performed in triplicate, confirmed in a biological replicate. Bottom panel) The quantification of 5mC was performed as above; DNA methylation was significantly higher in mutant than in WT D2HGDH cells (p<0.001, one-way ANOVA, p<0.05, Bonferroni's multiple comparison post-test). The data show represent the combined values of three biological replicates, performed in triplicate or duplicate. The western blot data shown in a) and b) were confirmed in biological replicates at least three times, and all results independently validated with a transient transfection model (Figure 1).



Supplementary Figure 8. Transient and stable knockdown (KD) of D2HGDH in HEK-293 cells. a) Transient transfection of two siRNA oligonucleotides directed at D2HGDH or a control siRNA led to increase in the methylation levels of H3K4, H3K9, H3K27 and H3K36; but not in H3K79 which is not regulated by α -KG-dependent HDMs. b) Upon exposure to hypoxic conditions for 16h, cells with stable shRNA-based KD of D2HGDH showed marked suppression of hydroxylated HIF1 α with consequent accumulation of total HIF1 α . Efficacy of the transient (siRNA) or stable (shRNA) KD of D2HGDH is shown by western blot (a and b). Note that the transient KD only partially suppresses D2HGDH expression (~60%). Densitometric quantifications are shown at the bottom. c) The levels of the DNA marks 5hmC and 5mC (top and bottom panels) were significantly lower and higher, respectively, in D2HGDH-KD cells than their controls (p<0.0001, ANOVA); d), e) and f) show that the transient, partial, KD of D2HGDH significantly modify D2-HG (p= 0.04, ANOVA), α -KG (p=0.02, ANOVA), but not L2-HG levels (p=0.4, ANOVA), as determined by LC/MS. The 5hmC and 5mC measurements shown represent the mean and SD of five data points derived two independent assays. The LC/MS data shown is the mean of an experiment performed with two replicates; similar results were obtained in an independent assay performed with a single replicate.



Supplementary Figure 9. D2HGDH expression and IDH activity a) Left - Transient expression of increasing amounts of WT D2HGDH significantly and progressively increased IDH activity in comparison to that of MSCV-expressing isogenic cells (p<0.0001 ANOVA, p<0.05 Bonferroni's Multiple Comparison post-test). Middle and Right panels - Transient knockdown of D2HGDH in the B cell lymphoma cell lines significantly decreased IDH activity in comparison to isogenic controls (p<0.0001; p=0.0003; ANOVA, for OCI-Ly8 and Ramos, respectively - p<0.05 Bonferroni's Multiple Comparison post-test). In **b)** western blot-based examination of D2HGDH expression in the proteins used for the IDH activity assay (shown in a) confirms its progressive elevation in the transient transfection of HEK-293 cells, and partial knockdown in the B cell lymphoma cell lines OCI-Ly8 and Ramos. Densitometric analysis is shown below the western blot.



Supplementary Figure 10. IDH1 and IDH2 expression in models of gain and loss of D2HGDH and following exposure to synthetic cell-permeable α-KG. a) Western blots show that the expression of IDH1 is not modified by D2HGDH knockdown (left panel), its transient or stable ectopic expression (middle panels), or exposure to the cell-permeable octyl-α-KG (right panel). b) Western blot analysis show IDH2 downregulation in D2HGDH knockdown HEK-293 cells (left panel), and its upregulation in models of D2HGDH transient or stable expression (middle panels) or upon exposure to the octyl α-KG (right panel). Densitometric quantifications are shown at the bottom of the western blots. These assays were repeated two to four times. c) Left panel - real-time RT-PCR of HEK-293 cells with stable D2HGDH knockdown show a significant downregulation of IDH2 (p=0.01, ANOVA). Middle - quantification of IDH2 by real-time RT-PCR demonstrate a significantly higher IDH2 expression in D2HGDH-WT cells than in the empty-vector isogenic controls. (p=0.01, two-tailed Student's t-test). Right quantification of IDH2 by real-time RT-PCR demonstrate a significantly higher IDH2 expression in HEK-293 cells exposed to synthetic α -KG than vehicle control (p<0.001, two-tailed Student's t-test). The data shown in c) (left and middle panels) represent mean and SD of three independent biological replicates (each assay performed in triplicate), displayed as relative expression (sh-ctrl vs. sh-D2HGDH, or MSCV vs. D2HGDH-WT); the data shown in the right panel is the mean -/+ SD of a representative assay performed in triplicate - two independent biological replicates were completed and yielded similar results. In all instances, IDH2 expression was normalized to that of a housekeeping gene TBP, relative quantification achieved by calculating $\Delta\Delta$ Ct, and expression defined as 2^{- $\Delta\Delta$ Ct}, where cells expressing control vector, or vehicle, represent the baseline.



Supplementary Figure 11. D2HGDH levels in models of IDH2 ectopic expression or knockdown. a) Western blot analysis shows that ectopic expression of IDH2 in models of D2HGDH knockdown (KD#3 and KD#5) does not change its expression – compare levels of D2HGDH in KD#3 and KD#5 MSCV-only cells vs. KD#3 and KD#5 in IDH2 cells. Expectedly, the D2HGDH levels are lower in KD#3 and KD#5 cells than in control pSilencer/MSCV cells. b) shRNA-mediated knockdown of IDH2 did not change D2HGDH expression levels in MSCV control cells (left panel) or in their isogenic counterparts expressing WT D2HGDH (right panel). Expectedly, the D2HGDH-WT cells than in MSCV controls.



Supplementary Figure 12. Interplay between D2HGDH, α -KG and IDH2 in DLBCL. a) HPLC-ESI-MS-based quantification of α -KG and D2-HG in 14 parental DLBCL cell lines showed significantly lower levels of α -KG in D2HGDH mutant DLBCLs than in WT cells, but no significant difference in the abundance of D2-HG. For each cell line, the data shown represent the median value of three independent assays, each performed in triplicate (p=0.02, two-tailed Student's t-test). b) Western blot analysis of IDH2 in a set of 14 DLBCL cell lines, including four D2HGDH mutant and 10 wild-type. Densitometric quantification of IDH2 (normalized by β -actin) is shown below the blots and in graphic display with its statistical significance denoted (Mann-Whitney test). The metabolite quantification in a) was normalized by protein concentration.



Supplementary Figure 13. Genetic modulation and functional analysis of D2HGDH-mutant DLBCL cell lines. Isogenic models of stable expression of an empty vector (MSCV) or WT D2HGDH were generated by retrovirus transduction in four independent D2HGDH-mutant DLBCL cell lines. a) Ectopic expression of D2HGDH decreased H3K4 and H3K9 methylation in all four models, an effect that was largely reversed by exposure to 1mM of dimethyloxalylglycine (DMOG), a competitive inhibitor of α -KG. b) The Hydroxylation of proline 402 in HIF1 α -was elevated (top panel) and total HIF1 α expression decreased (bottom panel) by expression of WT D2HGDH – in both instances the values were returned to baseline following exposure to DMOG. c) Quantification of 5hmC or 5mC show that ectopic expression of D2HGDH-WT in DLBCL mutant cells significantly elevated the abundance of 5hmC marks (top) (p<0.0001, ANOVA) and lowered total DNA methylation (5mC levels) (bottom) (p<0.0001, ANOVA). For both measurements, the effects of D2HGDH were largely abrogated by exposure to DMOG. The abundance of these modifications are reported as relative values normalized by a positive control, a polynucleotide containing 20% 5hmC or 50% 5mC. Experiments show in a) and b) were repeated twice; data in c) represent the mean and SD of a representative experiment (out of two independent assays) performed in triplicate. d) Stable ectopic expression of D2HGDH in the four D2HGDH-mutant DLBCL cell lines induced IDH2 expression. Densitometric quantification (normalized by β -actin) is shown at the bottom of the western blots



--72kd

--56kd

--43kd

-34kd

-72kd

-56kd

-43kd

-34kd



Supplementary Figure 14. Full scans of uncropped blots presented in the main paper. Red boxes indicate the cropped regions. Molecular weight markers are indicated in kDa.





















Supplementary Figure 14 - continued

250

20 -

15 -

actin for the octyl-z-kg

--75kd

-50kd

--37kd --25kd

За

3b







Supplementary Figure 14 - continued

3e





4b







6a



Supplementary Figure 14 - continued



5b





















--17kd --11kd

--26kd

--17kd

--11kd





H3











Supplementary Table 1 - D2HGDH mutational status in I	DLBCL
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Sample ID 517	Ex2	Ex3 0.293-18A>G	Ex4 WT	Ex5 WT	Ex6 Ex7 .c.685-9T>CT WT wr	Ex8 c:012GSAG.p.Val33888.c.01082C>TC.p.Ala361Val.c.1107T>CT;p.Asp369Asp c:1027C=AG.p.Gb/25552cc	Ex9 WT	Ex10 c.1307-24A>G 1307-24A>G
642 865	c.292+28T>GT c.292+28T>GT c.292+28T>GT	. 293-18A>AG . 293-18A>AG	WT c.490+40T>CT	WT WT	C.685-9T>CT WT C.685-9T>C WT	c:1082CS-TC p.Ala361Val c:1082CS-TC p.Ala361Val c:1012GS-AG p.Val33888c.c:1082CS-TC p.Ala361Val c:1012GS-AG p.Val38888c.c:1082CS-TC p.Ala361Val	WT WT	c.1307-24A>GA c.1307-24A>GA c.1307-24A>GA
1057 1143 1309	C28242813G1 C292428T>GT C292428T>GT	WT WT	c.490+4015C1 WT c.351-46G5AG;c.490+40T5CT	WT WT	C.885-915C1 W1 WT c.685-975CT WT	e.102GSAG p.Var3888e e.11071SCT; p.Asp36MA8p WT WT	WT WT	c.1307-24ASG WT c.1307-24ASGA
1320 0 1326 0 1423 0	2.164G>AG,p.Arg55GIn c.292+28T>G 2.43C>CG, p.Arg15GIy c.164G>AG,p.Arg55GIn 2.43C>CG, p.Arg15GIy c.164G>AG,p.Arg55GIn c.292+28T>GT	c.293-18A≻G WT WT	c.490+40T>CT c.490+40T>CT WT	WT WT WT	c.685-9T>C WT c.685-9T>CT WT WT WT	c.1012G>AG p.Val338lie c.1082C>TC p.Ala361Val_c.1107T>CT; p.Asp369Asp c.1012G>AG p.Val338lie WT	c.1306+68T>CT c.1306+68T>CT WT	c.1307-24A>GA WT WT
1479 c 1650 c	164GxAG,p.Arg55Gin c.292+28T>GT 143C>CG, p.Arg15Giy c.292+28T>GT c.292+28T>GT	WT : 293-18A>AG : 293-18A>G	WT WT	WT WT	WT WT c.685-9T>CT WT c.685-9T>C WT	WT. c.1082C>TC p.Ala361Val WT	WT WT	WT 0 1307-244 \G
2202 2216	c.292+28T>GT WT	: 293-18A>AG WT	WT WT	WT WT	c.685-9T>CT WT WT WT	c.1082C>TC p.Ala361Val WT	c.1306+68T>CT WT	c.1307-24A>GA c.1377C>AC.p.Pro459Pro WT
2323 2485 2633	C292+2815G1 NT C292+28T5GT	W1 WT 0.293-18A>AG	WT WT	WT WT	C.685-915C1 W1 WT c.685-915C WT	W1 WT c.1082C>T p.Ala361Val	c.1306+681>C1 WT c.1272G>AG p.Pro424Pro	c.1307-24ASGA WT c.1307-24ASGA
2992 3002 3271	1-1-91 C>GC c.292+28T>GT c.292+28T>GT 154G>4G p.4m55Gip.c.292+28T>GT	2.293-18A>AG WT 1.293-18A>AG	c.490+40T>CT WT c.490+40T>CT	WT WT	c.685-9T>CT WT WT WT c.685-9T>CT WT	c.1012G>AG p.Val338lie WT c.107TsCT: p.Asr369Asp.	WT WT c 1305468TxCT	WT c.1307-24A>G c.1377C>AC,p.Pro459Pro c.1307-24A>G
3279 3410 3416	c.292+28T>GT 1164G>AG,p.Arg55GIn 1164G>AG,p.Arg55GIn c.292+28T>GT	WT 2293-18A>G WT	WT c.490+40T>CT c.490+40T>CT	WT WT	WT WT c.685-9T>C WT WT	WT c.1012GsAG p.VaI3388e c.1082C>TC p.Ala361Va WT	WT WT	c.1307-24A>GA c.1377C>AC.p.Pro459Pro WT WT
3466 (3522) 3533 (164GxAG,p.Arg55Gln c.292+28T>GT WT 164GxAG,p.Arg55Gln c.292+28T>GT	WT c.293-18A>AG WT	WT c.490+40T>CT c.490+40T>CT	WT WT	WT WT c.685-9T>CT WT c.685-9T>CT WT	WT c.1012G>AG p.Val338lle WT	WT c.1306+68T>CT c.1306+68T>CT	WT c.1307-24A>G c.1307-24A>GA c.1388A>TA.p.Glu463Va
3717 3832 4018	c.292+28T>GT 164G>AG,p.Arg55Gin c.292+28T>GT 164G>AG,p.Arg55Gin	WT 0.293-18A>GA	WT WT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1012G>AG.p.Val338lie.c.1082C>TC.p.Ala361Va c.1082C>T.p.Ala361Val c.1082C>T.p.Ala361Val	WT WT	c:1307-24A>GA c:1307-24A>GA WT
4021 0 4236 0 4350 0	164G>AG,p.Arg55GIn c.292+28T>GT 164G>AG,p.Arg55GIn c.292+28T>GT 292+28T>GT	WT 0.293-18A>GA	c.490+40T>CT c.490+40T>CT WT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1012G>AG p.Val3388ie c.1107T>CT; p.Asp360Asp c.1082C>T; p.Ala381Val	WT WT	c.1307-24A>G c.1307-24A>GA WT
4375 4450 4470	164G>AG,p.Arg55GIn c.292+28T>GT 1292+28T>GT 164G>AG,p.Arg55GIn c.292+28T>GT	WT 0.293-18A>GA	WT 0.490+40T>CT	WT WT	WT WT WT WT c.685-9T>CT WT	WT WT WT	WT WT	WT c.1307-24ASG WT
4494 4522 4554	1292+28T>GT 1164G>AG,p.Arg55GIn c.292+28T>GT 1292+28T>GT	c.293-18A>GA c.293-18A>GA c.293-18A>GA	WT c.490+40T>CT WT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1082C>T p.Ala361Val WT WT	WT WT	c.1307-24A>G c.1307-24A>GA c.1307-24A>GA
4756 0 5028 0 5058 0	11-91 C>GC c.292+28T>GT 11-91 C>GC c.292+28T>GT 1292+28T>GT	WT WT c.293-18A5AG	WT WT WT	WT WT	WT WT WT WT c.685-9T>CT WT	WT WT c1082C>CT.p.Ala361Val	WT WT	c.1307-24A>GA c.1377C>AC.p.Pro459Pro WT c.1307-24A>GA
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5186 5190 5204	WT 2.164G>AG,p.Arg55GIn WT	c.293-18A>G c.293-18A>GA c.293-18A>GA	c.490+40T>CT c.490+40T>CT WT	WT WT WT	c.685-9T>C WT c.685-9T>CT c.774G>AG, p.Ser258Ser WT c.685-9T>CT WT	e.1082C>TC p.Ala361 Val c.1012G>AG p.Val388ie e.1082C>TC p.Ala361 Val	c.1306+68T>CT c.1306+68T>CT WT	c. 1307-24A>GA c. 1307-24A>GA c. 1307-24A>GA
5234 5278 5283	12924281>GT NT NT	:.293-18A>GA :.293-18A>GA :.293-18A>GA	c.490+40T>CT WT WT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1012GsAG p.Val338lle c.1107TsCT; p.Asp369Asp c.1082CsTC p.Ala361Val WT	c.1276G>AG,p.Ala426Thr c.1306+68T>CT WT WT	WT c.1307-24A>GA c.1307-24A>GA
5364 0 5370 0 5485 0	2.164G>AG,p.Arg55Gin 2.164G>AG,p.Arg55Gin c.292+28T>GT 2.164G>AG,p.Arg55Gin c.292+28T>GT	WT 2.293-18A>GA WT	WT WT	WT WT	WT c.685-9T>CT; c.853+48G>AG WT WT WT	6.1064GxAG p.Gly355Ser 6.1012GxAG p.Val338lie WT	WT WT WT	c.1307-24A>GA WT c.1307-24A>GA c.1377C>AC,p.Pro459Pro
5782 C	2.164GsAG,p.Arg55Gin c.29242815G1 2.164GsAG,p.Arg55Gin c.292428TsGT 2.292428TsGT	2293-18ASGA 2293-18ASGA WT	w1 c.490+40T>CT WT	WT WT	C.685-915C1 W1 c.685-915CT WT WT	W I c.1012G>AG p.Val338lle WT	WT C.1306+68T>CT	C.1307-24ASGA WT C.1307-24ASGA
6290 0 6614 0	2.164G>AG,p.Arg55Gin c.292+28T>GT 2.164G>AG,p.Arg55Gin c.292+28T>GT 2.164G>AG,p.Arg55Gin c.292+28T>GT	293-18A>G 293-18A>G 293-18A>G	c.490+40T>CT c.490+40T>CT	WT WT	WT c.685-9T>C c.685-9T>C WT c.685-9T>C WT	1082C>TC p.Ala361Val 1082C>TC p.Ala361Val 1082C>TC p.Ala361Val 1082C>TC p.Ala361Val	c.1306+68T>CT c.1306+68T>CT	c.1307-24A>GA c.1307-24A>G WT
6902 0 6971 0	12924281>GT 1292428T>GT 164GsAG, p.Arg55Gin c.292428T>GT	WT 2293-18A>GA 2293-18A>GA	c.490+40T>CT c.490+40T>CT	WT WT	C685-915C WT C685-915CT WT C685-915CT WT	c.1082CS1 p.Pai361Val WT c.1012G>AG p.Val338lie c.1012G> v. tionetuut	WT c.1276G>AG,p.Ala426Thr c.1306+68T>CT WT	c.1307-24A>G WT
7089 0	129242813G1 164GsAG,p.Arg55Gin c.292428TsGT 1292428TsGT	2293-18A>G 2293-18A>G	c.490+40T>C c.490+40T>C	WT WT	C.685-915CT WT C.685-915CT WT C.685-915C WT	c:102CS-1p.Aas361Vai c:1012CS-AG p.Val3388c c:1104+39C>TC c:1012CS-AG p.Val3388c c:1082C>TC p.Ala361Vai c:1107T>CT; p.Asp369As; cave	0.1306+68T>C 0.1306+68T>C	c.1307-24A>G c.1307-24A>G c.1307-24A>G
7518 0	19945346,0048356110,2324281561 1292428T5GT 1292428T5GT	2.293-18A>G 2.293-18A>GA	WT c.490+40T>C	WT WT	c.685-9T>C WT c.685-9T>CT WT	6.1082C>TC p.Ala361Val c.1012G>AG p.Val3388e	WT c.1306+68T>CT	c.1307-24A>GA c.1307-24A>G c.1377C>AC,p.Pro459Pro
7924 c 7970 c 7987 c	1292+28T>GT 1292+28T>GT 1164G>AG,p.Arg55GIn c.292+28T>GT	c.293-18A>G c.293-18A>GA c.293-18A>GA	c.490+40T>C WT WT	WT WT WT	c.685-9T>C WT c.685-9T>CT WT c.685-9T>CT WT	c.1012GsAG p.Val338lie c.1082CsTC p.Ala361Val c.1082CsTC p.Ala361Val	c.1306+68T>C WT WT	c.1307-24A>G WT WT
A1 0 A2 A3 0	164G>AG p.Arg55Gin, c.292+28T>GT c.292+28T>GT 164G>AG p.Arg55Gin, c.292+28T>GT	WT 2.293-18A>GA 2.293-18A>GA	WT c.490+40T>CT c.490+40T>CT	WT c.634C>TC p.Arg212Trp WT	WT WT c.685-9T>CT WT c.685-9T>CT WT	WT c.1012G>AG p.Val338lle c.1012G>AG p.Val338lle	WT c.1306+68T>CT c.1306+68T>CT	WT c.1307-24A>GA c.1307-24A>GA
A4 0 A5 0	292+28T>GT 2164G>AG p.Arg55GIn, c.292+28T>GT 2164G>AG p.Arg55GIn, c.292+28T>GT	WT 293-18A>GA 292-19A>G	WT c.490+40T>CT c.490+40T>C	WT WT	WT WT c.685-9T>CT WT	WT c.012G>AG p.Val338lle c.1013G>A p.Val338lle	0.1306+68T>CT 0.1306+68T>CT	c.1307-24A>GA c.1307-24A>GA
B1 B2	2292428T>G	2.293-18A>GA 2.293-18A>GA	WT c.490+40T>CT	WT WT	c.685-9T>CT WT c.685-9T>CT WT	c.1012G>FC p.AlaS61Val c.1012G>AG p.Val338lie	WT c.1306+68T>CT	c.1307-24A>GA, c.1377C>AC p.Pro459Pro c.1307-24A>G, c.1377C>AC p.Pro459Pro
B3 B4 \ B5 \	c292+28T>GT NT NT	c.293-18A>GA WT WT	WT WT WT	WT WT WT	c.685-9T>C WT WT WT WT WT	WT WT WT	WT WT	c.1307-24A>GA WT c.1307-24A>GA
B6 \ C1 0	NT 1.164G>AG p.Arg55Gin, c.292+28T>G n 292+28T>GT	WT 2.293-18A>G 2.293-18A>G	WT c.490+40T>CT WT	WT WT	WT WT c.685-9T>C WT c.685-9T>CT WT	WT c.1012G>AG p.Val338lle WT	WT c.1306+68T>CT WT	WT c.1307-24A>G c.1307-24A>G
C3 C4	164G>AG p.Arg55Gin, c.292+28T>GT MT 164G>AG p.Arg55Gin, c.292+28T>GT	293-18A≻G 293-18A≻GA 292-18A≻GA	WT c.490+40T>CT c.490+40T>CT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1082C>TC p.Ala361Val c.1012G>AG p.Val3388e c.1012G>AG p.Val3388e	0.1306+68T>CT 0.1306+68T>CT 1306+68T>CT	c.1307-24A>GA c.1307-24A>GA c.1307-24A>GA
C6 0	164G>AG p.Arg55Gin, c.292+28T>GT 2.164G>AG p.Arg55Gin, c.292+28T>GT 2.292+28T>GT	WT WT	WT WT	WT WT	WT WT WT WT	C 1012GSAG p.Val2388ie C 1012GSAG p.Val338ie	WT c.1306+68T>CT	c.1307-24A>GA c.1307-24A>G
D2 0 D3 0 D4 0	2.164GsAG p.Arg55Gin, c.292+2815G1 2.164GsAG p.Arg55Gin, c.292+2815G 2.164GsAG p.Arg55Gin, c.292+2815GT	0.293-18A>GA 0.293-18A>G 0.293-18A>GA	0.490+4015C1 WT WT	WT WT	c.685-915C1 W1 c.685-975C WT c.685-975CT WT	c.1012G>AG p.Val3388e.c.1082C>TC p.Ala361Val WT	c.1306+681>C1 c.1306+68T>CT c.1306+68T>CT	c.1307-24ASGA c.1307-24ASGA c.1307-24ASG
D5 0 D6 0	2.164GxAG p.Arg55Gin, c.292+28TxGT 2.164GxAG p.Arg55Gin, c.292+28TxGT 2.164GxAG p.Arg55Gin, c.292+28TxG	c.293-18A>G c.293-18A>GA	c.490+40T>C c.490+40T>CT WT	WT WT	c.685-9T>CT WT c.685-9T>CT WT c.685-9T>CT WT	c.1012G>A.p.Val338lie c.1012G>AG.p.Val338lie WT	c.1306+68T>CT c.1306+68T>CT WT	c.1307-24A>G c.1307-24A>GA c.1307-24A>GA
E2 0 E3	164G>AG p.Arg55Gin, c.292+28T>GT c.292+28T>GT c.292+28T>GT	c.293-23A>TA, c.293-18A>GA c.293-18A>G c.293-18A>G	c.490+40T>CT c.490+40T>CT	WT WT	0.685-9T>CT WT 0.685-9T>C WT 0.685-9T>C WT	c.1012G>AG p. Val338lie c.1012G>AG p. Val338lie Wrt	0.1306+68T>CT 0.1306+68T>CT	c.1307-24A>G c.1307-24A>G c.1307-24A>G
E5 V	WT 164GxAG p.Arg55Gin, c.292+28TxGT	WT 293-23A>TA, c.293-18A>GA	WT c.490+40T>CT	WT WT	WT WT c.685-9T>CT WT	WT c.1012G>AG p.Val338lie	WT c.1306+68T>CT	WT c.1307-24A>GA
F1 0 F2 0 F3	2.164GsAG p.Arg55Gin, c.292+2815G1 2.164GsAG p.Arg55Gin, c.292+28TsGT c.292+28TsG	2.293-18A>GA WT 2.293-18A>GA	0.490+4015C1 WT WT	WT WT	C.885-915C1 W1 WT WT c.685-915CT WT	6.1012GSAG p.Val33886 WT c.1038C>TC p.Asn346Asn, c.1082C>TC p.Ala361Val	WI WT c.1306+68T>CT	c.1307-24ASGA WT c.1307-24ASGA
F4 F5 F6	c.292+28T>GT 2.164G>AG p.Arg55GIn, c.292+28T>GT Fw not good and there is no reverse	c.293-18A≻G c.293-18A≻GA c.293-18A≻GA	WT c.490+40T>CT WT	WT WT WT	c.685-9T>C WT c.685-9T>CT WT c.685-9T>CT WT	WT c.1012G>AG p.Val338lie c.1082C>TC p.Ala36lVal	WT c.1306+68T>CT c.1306+68T>CT	c.1307-24A>G c.1307-24A>GA c.1307-24A>G
G1 G2 G	2.164G>A p. Arg55Gin, c.292+28T>G 2.164G>AG p.Arg55Gin, c.292+28T>G 2.164G>AG p.Arg55Gin, c.292+28T>G	:.293-18A≻G :.293-18A≻GA WT	c.490+40T>C WT WT	WT WT	c.685-9T>C WT c.685-9T>CT WT	c.1012G>AG p.Val338lle, c.1107T>CT.p.Asp369Asp c.1082C>TC p.Ala361Val WT	c.1306+68T>C WT WT	c.1307-24A>G c.1307-24A>GA WT
G4 G5 G5	164G>AG p.Arg55Gin, c.292+28T>G 164G>AG p.Arg55Gin, c.292+28T>G 2624/32T-G	0.293-18A≻G WT WT	WT WT	WT WT	c.685-9T>C WT WT WT	c.1012G>AG p.Val338lie,c.1082C>TC p.Ala361Val WT	c.1306+68T>C WT	c.1307-24A>G c.1307-24A>GA
H1 0 H2 0	164G>AG p.Arg55Gin, c.292+28T>G 164G>AG p.Arg55Gin, c.292+28T>G	WT WT	WT WT	WT	WT WT WT WT	WT WT	WT WT	WT c.1307-24A>GA, c.1377C>AC p.Pro459Pro
H3 0 H4 H5	. юнаэна р.Агдээціп, с.202428T>G 0.292428T>GT 0.292428T>GT	2233-18A5GA 0.293-18A5GA WT	c.490+4015G1 c.490+40T5GT WT	WT	c.685-91>CT WT C.685-97>CT WT WT	c. 1012G>AG p.Val3388e C.1012G>AG p.Val3388e WT	c.1306+68T>CT WT	c.1307-24A5GA c.1307-24A5GA WT
H6 1 DHL10 0 DHL16 1	NA 1292+28T>GT WT	WT WT	c.490+40T>CT WT WT	WT WT	c.685-9T>CT WT WT WT WT WT	c.1012G>AG p.Val338lle WT WT	na WT WT	WT c.1307-24A>GA WT
DHL2 0 DHL4 V	164G>AG,p.Arg55GIn NT 2002428T-GT	:.293-18A⊳GA :.293-18A⊳G :.293-18A⊳G	WT WT	WT WT	0.685-9T>CT WT 0.685-9T>C WT 0.685-9T>C WT	c.1012G>GA.p.Val338lie c.1082C>TC.p.Ala36liVal	WT WT	c.1307-24A>GA WT c.1307-24A>G
DHL6 C	: 164G>AG,p.Arg55GIn c.292+28T>GT	2293-18A>G	c.490+40T>CT WT	WT WT	C.685-9T>C WT WT WT	a 1082C>TC p.Ala361Val WT	c.1262G>AG, p.Arg421His WT	c. 1307-24A>GA WT
Farage V HBL-1	2 гонахна,р.нидобыл с.2824281561 WT 1292428T>G	WT 293-18A>G	WT	WT	WT WT 6.685-97>C WT	W1 WT c.1082C>TC p.Ala361Val	WT WT	WT
HT K1106P K422	NT 2164G>AG,p.Arg55GIn 2164G>AG,p.Arg55GIn	WT 0.293-18A>GA	WT WT	WT WT	WT WT WT WT c.685-9T>CT WT	WT WT 4.1082C>TC p.Ala361Val	WT C.1306+68T>CT	WT WT c.1307-24A>GA
Ly1 c	2.164G>AG,p.Arg55GIn 2.164G>AG,p.Arg55GIn c.292+28T>GT	WT 293-18A>GA	c.490+40T>CT c.490+40T>CT wrt	WT WT	WT WT 6.685-9T>CT WT 6.585-9T-CT	WT WT wr	c.1306+68T>CT c.1306+68T>CT	c.1307-24A>GA c.1307-24A>G
Ly19 V Ly3 d	MT 2.164G>AG,p.Arg55GIn c.292+28T>GT	WT 2293-18A>GA	WT c.490+40T>CT	WT WT	WT WT C.685-9T>CT WT	кт. WT WT	WT c.1306+68T>CT	WT c.1307-24A>G
Ly4 \ Ly7 c Ly8 c	11-91 C>GC c.292+28T>GT 1292+28T>GT	0.293-18A>G 0.293-18A>GA	c.490+40T>C WT	WT	C.685-9T>C WT C.685-9T>CT WT	ич і c.1012G>A.p.Val338lie c.1107T>CT; p.Asp369Asp c.1082C>TC p.Ala361Val	w1 c.1276G>AG,p.Ala426Thr c.1306+68T>CT WT	c.1307-24A>G c.1307-24A>GA
NU-DHL1 C NU-DUL1 C Pfeiffer	1292+28T>GT 1164G>AG,p.Arg55GIn WT	293-18A>GA 293-18A>GA WT	WT c.490+40T>CT	WT WT	c.685-9T>CT WT c.685-9T>CT WT WT WT	c.1082C>TC p.Ala361Val c.1012G>A p.Val338lie WT	WT c.1306+68T>CT WT	WT c.1307-24A>GA WT
RC-K8 Toledo	292428T>GT 2164G>AG,p.Arg55Gin c.292+28T>GT 2164G>AG,p.Arg55Gin c.292+28T>G	293-18A>GA	WT c.490+40T>CT c.490+40T>CT	WT WT	c.685-9T>CT WT c.685-9T>CT WT	c.1082C>TC p.Ala361Val WT c.1013G=A.p.Wx/228/in	WT c.1306+68T>CT c.1306+68T>CT	c.1307-24A>GA c.1307-24A>GA
USC-DHL1 C WSU-NHL C	2.164GxAG,p.Arg55Gln c.292+28T>GT 2.164GxAG,p.Arg55Gln c.292+28T>GT 2.164GxAG,p.Arg55Gln c.292+28T>GT	WT WT	0.392delG; Gly131fsX21	WT WT	TW T WT WT WT	wT c.1064GxAG p.Gly355Ser	WT WT	WT c.1307-24A>GA
r 7 7	x82191976: c.1-91 C-OC=2.7% (4%) x4675887: c.43C-CC, p.Arg1503=2% (3.8%) x7744054: c.446G-AAD p.Arg5501a=46.8% (21.7%) x82191977: c.292+28T>OT= 77% (73%)	134073889: c.293-18A>GA=61.4% (5 13145731647: c.293-23A>TA=1.3% (:TMP-ESP-2-24261803: c 351-46G>A0 fis78147778: c 400+40T>CT= 39.1% (3= 0.6% (0.02 - 0.04) 22%)	Is4234007: c.885.0T>CT= 68.2% (52.7%) TMP-ESP-2-343884213: c.774G>AG, p.Sar3585ar= 0.6% (0. Is180686843: c.853448G>AG= 0.6% (0.001%)	rs1108830: c.1012G2-AG p. Val33816= 31% (21%) 01rs139251130: c.1083G2-AG p.Gly35558a+ 0.6% (0.001%) s1105273: c.08262-TD p.Aa8028C-TD p.Aa9380A39+ 6% (2.6%) rs141343442: c.1107Ts-CT p.Aa9369As9+ 6% (2.6%)	rs139611034: c.1262G>A, p.Arg421His=0.6% (0.01 TMP-ESP-2-242695395: c.1272G>AG, p.Pre424Pro rs146578303: c.1276G>AG, p.Aia426Thr= 2% (<0.01 rs62192024: c.1306+68T>CT= 37.1% (33.7%)	ns6756901: c.1307-24A>GA= 67.5% (62.1%) ns143940595: c.1377C>AC p.Pro459Pro= 6% (0.01%) %)

Supplementary Table 2 - Copy number at the D2HGDH locus

	Q	PCR	(Q-PCR	MI	.PA	Q-	PCR	Q	-PCR	Q	-PCR	N	/ILPA	N	1LPA	c	Q-PCR	M	LPA	м	ILPA
	Upstr	eam #1	Ups	tream #2	E	(2	E	x3	E	Ex4		Ex5		Ex6	1	Ex7		Ex8	E	x9	E	x10
Sample ID	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev	Mean	Std-dev
A01	0.78	n/a	0.80	n/a	0.85	0.18	0.88	n/a	1.21	n/a	1.02	n/a	0.92	0.16	1.10	0.69	1.05	n/a	1.81	1.02	0.94	0.55
DU1	0.80	0.11	0.77	0.06	1.44	0.16	0.76	0.07	0.77	0.12	0.71	0.11	1.50	0.21	1.50	0.14	0.97	0.40	1.22	0.24	0.00	0.31
D01	0.04	0.32	0.00	0.15	0.00	0.10	0.99	0.29	0.77	0.20	0.71	0.13	0.70	0.20	1.09	0.14	0.94	0.22	1.01	0.24	1.09	0.31
E01	1.07	0.13	0.04	0.05	1.00	0.00	0.99	0.07	0.80	0.12	1.13	0.07	1 15	0.10	1.00	0.38	1.13	0.20	0.95	0.03	1.25	0.20
E01	1.07	0.30	0.70	0.03	1.00	0.10	0.99	0.27	0.02	0.01	0.00	0.13	0.07	0.20	0.04	0.14	1.42	0.04	0.95	0.24	1.02	0.31
402	1.08	0.03	0.00	0.03	0.00	0.10	1.00	0.14	1 14	0.03	1.06	0.20	1.06	0.20	0.54	0.14	1.31	0.10	0.68	0.24	1.14	0.31
D02	1.00	0.21	0.05	0.11	1.00	0.00	1.65	0.00	0.60	0.10	0.05	0.14	1.00	0.10	0.73	0.14	0.95	0.20	0.00	0.04	0.02	0.10
H02	1.00	0.21	0.40	0.07	0.97	0.10	1.08	0.01	0.03	0.20	0.35	0.33	0.95	0.20	0.92	0.14	1 14	0.24	0.85	0.24	0.00	0.31
B03	0.96	0.00	0.70	0.01	1 12	0.02	0.97	0.04	1.00	0.03	0.82	0.01	1 15	0.03	0.85	0.02	1.09	n/a	1.28	0.08	1.05	0.01
D03	0.91	0.09	0.67	n/a	0.86	0.02	0.85	0.07	0.72	0.05	0.75	0.05	1.10	0.05	0.00	0.04	0.84	0.06	1.38	0.00	0.99	0.10
E03	1.21	0.16	0.95	0.10	1 12	0.05	1.20	0.11	0.82	0.08	0.88	0.48	1.36	0.00	0.91	0.48	1 10	0.00	0.88	0.85	0.00	0.31
E03	1.11	0.08	0.89	0.10	1 12	0.07	1.25	n/a	0.94	0.00	1.00	0.08	1.00	0.22	0.99	0.49	1.29	0.10	0.98	0.85	0.96	0.31
A04	1.17	0.09	0.93	0.07	1.52	0.22	1.16	0.13	0.80	0.07	0.94	0.09	1.15	0.18	1.59	0.70	1.15	0.09	2.08	1.03	1.02	0.55
C04	0.86	0.13	0.71	0.03	0.78	0.03	0.79	0.12	1.05	0.11	0.81	0.28	1.34	0.17	0.87	0.48	1.10	n/a	1.05	0.69	1.16	0.21
D04	1.08	0.15	0.84	0.10	1.09	0.11	1.27	0.83	1.56	1.33	0.90	0.11	1.25	0.23	0.75	0.24	1.29	0.19	0.89	0.45	1.03	0.03
G04	0.97	0.14	0.69	0.03	1.14	0.03	1.21	0.02	0.91	0.29	0.82	n/a	1.14	0.17	0.76	0.48	0.83	0.01	0.76	0.69	1.02	0.21
F04	1.63	0.34	0.93	0.20	0.99	0.10	1.38	0.29	1.18	0.29	1.03	0.22	1.26	0.14	0.84	0.42	1.08	0.29	0.95	0.63	1.10	0.21
H04	0.98	0.10	0.96	0.06	0.75	0.04	0.92	0.14	0.70	0.13	0.92	0.06	1.06	0.06	0.85	0.04	0.91	0.08	1.28	0.10	0.92	0.20
A05	1.02	0.02	1.05	0.03	0.99	0.05	1.09	0.10	1.43	0.41	1.08	0.02	1.34	0.07	1.08	0.06	1.10	0.01	1.60	0.12	1.02	0.20
B05	1.26	0.29	1.13	n/a	1.40	0.11	1.01	0.23	0.74	0.78	0.90	0.02	1.27	0.23	0.75	0.24	0.84	0.05	0.81	0.45	1.19	0.03
C05	0.99	0.04	0.80	0.04	0.90	0.12	1.25	0.16	0.96	0.09	0.96	0.05	0.84	0.23	1.16	0.24	1.26	0.06	1.70	0.46	0.85	0.05
D05	1.55	0.13	1.03	0.10	0.90	0.30	1.74	0.23	0.91	0.11	0.97	0.09	1.00	0.14	0.86	0.34	1.10	0.13	0.65	0.73	0.90	0.03
F05	0.92	n/a	0.71	0.09	0.89	0.11	1.13	0.11	0.91	0.18	0.88	0.04	1.38	0.24	0.82	0.24	1.18	0.03	1.00	0.46	0.88	0.04
G05	1.03	0.19	0.80	0.05	0.92	0.02	1.35	0.17	0.99	0.11	1.06	0.09	1.07	0.03	0.93	0.02	1.24	0.10	1.21	0.08	1.11	0.18
H05	0.82	0.19	0.75	0.03	1.01	0.11	1.25	0.16	1.23	0.25	1.18	0.04	1.32	0.24	0.90	0.24	1.52	0.13	1.11	0.46	1.08	0.05
SU-DHL4	0.99	0.08	0.79	0.07	1.04	0.03	1.30	0.07	1.03	0.03	1.01	0.07	1.04	0.12	1.02	0.09	1.09	0.04	1.12	0.06	0.90	0.03
SU-DHL5	0.87	0.18	0.82	0.01	1.04	0.03	1.17	0.04	1.05	0.02	0.84	0.15	0.92	0.12	0.91	0.09	1.00	0.16	0.98	0.06	0.93	0.03
SU-DHL7	0.93	0.08	0.85	0.01	1.43	0.08	1.05	0.01	1.03	0.12	0.97	0.03	1.26	0.14	1.31	0.11	1.09	0.05	1.29	0.09	1.21	0.07
SU-DHL8	1.06	0.06	1.01	0.03	1.06	0.12	0.74	0.05	0.80	0.02	0.80	0.05	0.72	0.15	2.54	0.30	0.88	0.02	3.26	0.37	1.29	0.15
SU-DHL9	0.94	0.06	0.89	0.04	1.05	0.04	1.09	0.15	1.50	0.12	1.33	0.06	1.02	0.20	0.74	0.48	1.39	0.06	0.67	0.85	1.00	0.31
SU-DHL10	0.86	0.06	0.86	0.03	1.01	0.61	0.96	0.23	1.56	0.19	1.32	0.05	1.09	0.55	1.14	0.58	1.37	0.07	1.05	0.50	1.08	0.47
SU-DHL-16	0.99	0.07	1.00	0.06	1.18	0.04	1.22	0.16	1.31	0.12	1.09	0.07	1.35	0.20	0.99	0.48	1.34	0.13	0.81	0.85	0.92	0.31
Farage	1.01	0.09	1.05	0.19	0.88	0.10	1.06	0.21	1.59	0.13	1.42	0.11	0.68	0.14	1.66	0.43	1.48	0.12	1.85	0.64	1.23	0.22
HBL1	0.83	0.05	0.83	0.03	1.36	0.06	1.15	0.27	1.02	0.02	1.03	0.04	1.11	0.13	1.18	0.10	1.03	0.04	1.16	80.0	0.94	0.04
HI Kamar 400	0.90	0.10	0.76	0.05	1.01	0.05	0.92	0.10	1.00	0.04	1.01	0.06	1.00	0.13	1.03	0.10	1.02	0.05	1.11	80.0	1.04	0.06
Karpas 422	0.89	0.08	0.83	0.05	1.01	0.01	1.28	0.19	1.20	0.06	1.20	0.07	0.99	0.12	0.99	0.08	1.12	0.05	1.01	0.06	0.88	0.01
Ly1	0.87	0.03	0.81	0.00	1.03	0.02	1.13	0.03	1.08	0.13	1.07	0.02	1.09	0.12	1.17	0.09	1.04	0.02	1.09	0.06	0.73	0.02
Ly/	0.87	0.12	0.85	0.02	1.01	0.04	0.83	0.21	0.75	0.01	0.82	0.03	0.88	0.13	0.90	0.09	0.84	0.01	0.95	0.07	0.89	0.04
Lyo	0.87	0.10	1.33	1.13	1.30	0.14	1.01	0.13	0.97	0.06	0.91	0.11	0.04	0.15	2.93	0.31	0.95	0.06	3.11	0.33	0.00	0.00
Ly10	1.03	0.31	0.07	0.11	1.19	0.02	1.03	0.15	1.09	0.17	1.01	0.11	0.70	0.14	2.03	0.27	0.94	0.10	2.99	0.20	1.00	0.00
Lyio	0.70	0.12	0.01	0.07	0.77	0.02	1.20	0.21	0.97	0.14	1.05	0.00	0.93	0.12	0.96	0.09	0.90	0.08	1.05	0.06	1.09	0.02
Dfoiffor	0.01	0.02	0.94	0.02	1.00	0.02	0.06	0.00	1.00	0.30	1.09	0.02	1.02	0.12	1.00	0.09	0.95	0.03	1.09	0.06	1.02	0.03
Tolodo	0.95	0.13	1 12	0.03	1.00	0.01	1.05	0.21	0.07	0.14	0.05	0.07	1.03	0.12	1.00	0.03	1.14	0.00	1.00	0.00	1.01	0.01
112032	0.52	0.03	0.33	0.40	0.50	0.02	0.78	0.16	0.45	0.05	0.33	n/a	0.51	0.03	0.51	0.02	0.54	0.04	0.62	0.00	0.53	0.10
WSILNHI	1 13	0.24	1.01	0.27	0.30	0.02	1 30	0.10	0.45	0.05	1 10	0.20	1.06	0.03	0.51	0.02	1 12	0.49	0.02	0.00	0.00	0.10
LISC-DHI 1	1.08	0.14	1 12	0.01	0.00	0.02	1.04	0.27	0.00	0.06	0.01	0.07	1 17	0.03	1.06	0.02	0.88	0.02	1 16	0.08	0.01	0.18
NU-DUI 1	0.73	n/a	1.06	n/a	1.00	0.61	1.52	n/a	n/a	n/a	1 40	n/a	1.01	0.55	1.03	0.58	1.26	n/a	0.98	0.50	0.90	0.48
NU-DH-1	1.78	0.36	1.12	0.23	1.09	0.02	2.42	0.71	1.08	0.33	1.08	0.23	1.15	0.03	1.11	0.02	1.38	0.29	1.17	0.08	1.19	0.18

The cell line U2932 showed a pattern of putative single copy loss across the entire D2HDGH locus and the upstream region (4 Mbp from D2HGDH's transcription start site). This finding was in agreement with an earlier report on the karyotype of this cell line (Leukemia and Lymphoma, 2002; 43: 2179 - 2189). The threshold for positive calls (copy number loss) was 0.7 or, when only one exon appeared to be targeted, 0.65.

Sample ID	unspiked % enriched	spiked % enriched	fold dilution	nmoles in solution	nmoles of α-KG/mg of protein	Relative abundance
MSCV	0.6031	0.3972	1.5184	48.2273	0.1901	0.46
D2HGDH -WT	0.5584	0.4568	1.2224	112.4016	0.4107	1.00
D2HGDH - R212W	0.5947	0.4429	1.3427	72.9414	0.3004	0.73
D2HGDH -A426T	0.5761	0.3829	1.5046	49.5471	0.1938	0.47
4h						
MSCV	0.6205	0.4651	1.3341	74.8230	0.2872	0.75
D2HGDH -WT	0.6045	0.4952	1.2207	113.2662	0.3850	1.00
D2HGDH - R212W	0.6112	0.4219	1.4487	55.7184	0.1898	0.49
D2HGDH -A426T	0.5941	0.3878	1.5320	46.9947	0.1809	0.47

Supplementary Table 3 - α -KG abundance in multiple D2HGDH models in [U-¹³C]-glutamine labeling assay

8h

Supplementary Table 4 – Summary of IDH V_{max} and K_m in multiple D2HGDH genetic models

Stable expression - gain-of-function

Cell ID	Total cell lysate - HEK-293				
	V_{max} (mean ± SD)	K_m (mean ± SD)			
MSCV (n=3)	29.7 (±0.51)	0.69 (±0.06)			
D2HGDH – WT (n=3)	33.9 (±0.74)	0.56 (±0.06)			
D2HGDH – G131X (n=3)	26.9 (±0.55)	0.76 (±0.08)			
D2HGDH – A208T (n=3)	27.4 (±0.50)	0.82 (±0.07)			
D2HGDH – R212W (n=3)	29.8 (±0.57)	0.78 (±0.07)			
D2HGDH – R421H (n=3)	26.1 (±0.50)	0.66 (±0.06)			
D2HGDH – A426T (n=3)	29.2 (±0.58)	0.62 (±0.06)			

Stable expression – loss-of-function

Cell ID	Total cell lysate – HEK-293 KD				
	V_{max} (mean ± SD)	K_m (mean ± SD)			
si-control (n=3)	30.4 (±0.38)	0.57 (±0.03)			
si-D2HGDH#3 (n=3)	25.0 (±0.29)	0.59 (±0.03)			
si-D2HGDH#5 (n=3)	25.9 (±0.28)	0.52 (±0.03)			

Transient expression - gain-of-function

Cell ID	Total cell lysate HEK-293 – transient transfection			
	V_{max} (mean ± SD)	K_m (mean ± SD)		
MSCV 0.5µg (n=3)	31.7 (±0.53)	1.33 (±0.10)		
MSCV 0.75µg (n=3)	31.5 (±0.56)	1.31 (±0.11)		
MSCV 1.0µg (n=3)	31.7 (±0.53)	1.33 (±0.10)		
D2 – WT 0.5µg (n=3)	33.5 (±0.34)	0.96 (±0.04)		
D2 – WT 0.75µg (n=3)	36.4 (±0.49)	1.12 (±0.07)		
D2 – WT 1.0µg (n=3)	38.1 (±0.39)	1.29 (±0.06)		

Transient expression - loss-of-function

Cell ID	Total cell lysate – OCY-Ly8 KD				
	V_{max} (mean ± SD)	K_m (mean ± SD)			
si-control (n=3)	48.7 (±1.29)	2.22 (±0.25)			
si-D2HGDH#3 (n=3)	40.2 (±0.69)	2.08 (±0.15)			
si-D2HGDH#5 (n=3)	41.9 (±0.93)	2.20 (±0.21)			

Transient expression - loss-of-function

Cell ID	Total cell lysate – Ramos KD				
	V_{max} (mean ± SD)	K_m (mean ± SD)			
si-control (n=3)	25.6 (±0.20)	1.06 (±0.04)			
si-D2HGDH#3 (n=3)	21.6 (±0.25)	1.05 (±0.06)			
si-D2HGDH#5 (n=3)	19.5 (±0.24)	0.89 (±0.05)			

Stable expression - loss-of-function

Subcellular fractions – HEK-293								
Cell ID	Mitoc	hondria	Cytosol					
	$V_{\rm max}$ (mean ± SD)	K_m (mean ± SD)	V_{max} (mean ± SD)	K_m (mean ± SD)				
si-control (n=3)	84.9 (±1.42)	1.01 (±0.07)	17.9 (±0.23)	0.67 (±0.04)				
si-D2HGDH#3 (n=3)	55.3 (±1.20)	1.10 (±0.10)	17.6 (±0.24)	0.72 (±0.04)				
si-D2HGDH#5 (n=3)	54.4 (±0.89)	0.88 (±0.06)	17.5 (±0.21)	0.80(±0.04)				

Transient expression - gain-of-function

	Subcellular fractions – HEK-293						
Cell ID	Mito	chondria	Cytosol				
	V_{max} (mean ± SD)	K_m (mean ± SD)	V_{max} (mean ± SD)	K_m (mean ± SD)			
MSCV (n=3)	58.8 (±1.18)	1.01 (±0.09)	17.6 (±0.26)	0.83 (±0.05)			
D2HGDH – WT (n=3)	84.3 (±1.66)	1.06 (±0.09)	17.7 (±0.26)	0.91 (±0.06)			

Supplementary Table 5.	IDH activity a	ssay in total	cell lysate

submitted in the second secon	Supplementary T	able 5. IDH ac	tivity assav ir	total c	ell lysates					
SCV 1 2 2 5 5 0:00.05 0.00077 14.04 0.007 1.0007 23.4 0.0007 1.0007 23.4 0.0007 1.0007 23.6 0.0007 1.0007 23.6 0.0007 23.6 0.000 0.0007 23.6 0.000 0.0011 23.6 0.0111 23.46 0.0111 23.46 0.0135 28.65		Stat	ble expression		,					
Correlation 4.340-minima Umax A.340-minima	HEOV		-		#0			#2		
0.25 0.0067 15.71 21.41 0.0065 1.5.75 0.22 0.0084 1.3.81 2.8.8 1 0.0067 18.40 Km 0.0065 1.7.85 Km 0.0064 1.5.4 Km 2.5 0.0107 2.2.5 0.05 0.0114 2.4.12 0.7.4 0.0112 2.2.6 Km 0.0064 1.5.4 Km 0.0064 1.5.4 Km 0.0064 1.5.4 Km 0.0112 2.2.6 Km 0.0113 2.2.5 0.0113 2.2.5 0.0113 2.2.5 0.0114 2.4.1 0.0113 2.2.5 0.0114 2.4.1 0.0115 2.2.5 0.0115 2.2.5 0.0114 2.4.1 0.0007 1.6.5 3.4.1 0.0007 1.6.5 3.4.1 0.0005 1.7.82 3.4.6 0.0115 2.3.5 0.0115 2.3.5 0.0115 2.3.5 0.0115 2.3.5.4 0.0115 2.3.5.4 0.0115 2.3.5.4 0.0115 2.3.5.4 0.0115 2.3.5.4 0.0115	d-iso(uM)	#1 A340nm/min	umol/min/ma	Vmax	#2 A340nm/min	umol/min/ma	Vmax	#3 A340nm/min	umol/min/ma	Vmax
0.5 0.0067 14.17 0.0065 17.76 0.0064 13.54 Km 2.5 0.0173 22.83 0.65 0.0114 24.12 0.74 0.0112 22.66 0.09 2.5 0.0133 22.50 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0135 22.56 0.0035 7.67 0.0035 7.67 0.0035 7.67 0.0035 7.68 34.61 0.0055 34.61 0.0124 22.16 0.0144 22.38 0.0144 22.38 0.0144 22.56 0.0155 34.61 0.0155 34.61 2.5 0.0144 22.38 0.0144 22.51 0.0144 22.51 0.0155 34.61 0.0155 34.61	0.25	0.0027	5.71	29.14	0.0022	4.65	30.02	0.0018	3.81	29.88
1 0.0087 15.40 Km 0.0088 17.98 Km 0.00112 22.38 Km 3 0.0130 22.33 0.0114 24.42 0.74 0.0112 23.84 0.0113 23.84 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 0.0135 22.85 Vraz 7.22 7.22 7.22 7.22 7.22 7.22 7.22 7.25 7.26 0.87 7.26 0.027 1.65 3.40 0.0152 22.76 0.0174 22.78 0.43 0.0152 22.78 0.0162 22.14 0.016 0.0122 22.81 0.0152 23.94 0.0152 22.14 0.0162 0.0152 22.51 0.0152 23.94 0.0152	0.5	0.0067	14.17		0.0065	13.75		0.0064	13.54	
2.5 0.017 2.2.83 0.65 0.0118 2.4.12 0.74 0.0111 2.3.48 0.9111 15 0.0123 2.2.53 0.0118 2.4.64 0.0111 2.3.48 0.0111 2.3.48 0.0135 2.2.62 0.0135 2.2.62 0.0135 2.2.62 0.0135 2.2.62 0.0135 2.2.62 0.0135 2.2.62 3.3 0.0135 2.2.62 3.3 0.0135 2.2.62 3.3 0.0026 5.5.5 3.401 0.0037 7.2.6 3.4.56 0.0120 0.0207 6.46 0.0144 0.0124 2.7.69 0.07 0.0137 3.0.69 Km 2.5 0.0126 2.3.14 0.616 0.0144 2.2.15 0.0135 3.3.41 0.0137 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 3.3.41 0.0152 2.5.9 0.0152 2.5.9 0.0152 2.5.9	1	0.0087	18.40	Km	0.0085	17.98	Km	0.0096	20.31	Km
5 0.0130 23.39 0.0114 23.46 0.0114 23.46 50 0.0133 28.14 0.0135 28.56 0.0135 28.56 20000 0.0135 28.56 0.0135 28.56 0.0135 28.56 20000 0.0135 28.56 0.0135 28.56 0.0135 28.56 20000 0.0072 6.16 0.0124 27.50 0.67 0.0137 0.0085 15.30 24.57 1 0.0077 5.16 0.0124 27.50 0.67 0.0124 27.58 0.67 0.0124 27.58 0.615 33.44 1 0.0044 22.15 0.0144 32.38 0.0155 34.61 0.0152 33.44 1 0.0144 32.15 0.0144 32.38 0.0152 33.61 0.0152 33.61 2400H G13X #1 #1 #2.58 0.0152 34.61 0.0152 33.61 0.0152 33.61 0.0152 33.61 0	2.5	0.0107	22.63	0.65	0.0114	24.12	0.74	0.0112	23.69	0.69
1 0.0133 2.230 0.0135 2.0.02 0.0136 2.2402 20 0.0135 2.856 0.0135 2.856 0.0135 2.856 20 0.0135 2.856 0.0135 2.856 0.0135 2.856 20 0.0097 2.166 Kn 0.0094 2.098 Kn 0.0137 2.856 0.0097 2.166 Kn 0.0094 2.098 Kn 0.0137 3.348 0.0141 0.0144 3.215 0.0128 2.814 0.0137 3.349 2.5 0.0128 2.814 0.0144 3.215 0.0133 3.349 2.6 0.0144 3.215 0.0144 3.215 0.0135 3.341 4.6 0.0144 3.215 0.0144 3.215 0.0135 3.341 4.6 0.0144 3.215 0.0144 3.215 0.0152 3.341 4.6 0.0034 6.8 0.0144 3.215 0.0152 3.341 </td <td>5</td> <td>0.0120</td> <td>25.39</td> <td></td> <td>0.0118</td> <td>24.96</td> <td></td> <td>0.0111</td> <td>23.48</td> <td></td>	5	0.0120	25.39		0.0118	24.96		0.0111	23.48	
25 0.0133 28.14 0.0134 28.56 0.0135 28.56 2HOPH VT rl rl cl 2 rl diamonal di	10	0.0135	28.50		0.0142	28.56		0.0140	29.62	
50 0.0131 28.56 0.0141 28.81 0.0135 28.56 2HOH W #1 K #2 K A30mm1m immolmit/m immolm	25	0.0133	28.14		0.0135	28.56		0.0135	28.56	
Participant I Participant Partinant Partinant Partina	50	0.0135	28.56		0.0141	29.83		0.0135	28.56	
CHOM WT #1 #2 #3 dis.(d)(M) Adhommin umolimining Vmax Adhommin umolimining Vmax Vmax Adhomin umolimining Vmax										
Cost (c) Participant Cost (c)	D2HGDH WT	#1 4240mm/min		Varian	#2		Vmm	#3		Veneu
CLS CLS <thcls< th=""> <thcls< th=""> <thcls< th=""></thcls<></thcls<></thcls<>	u-iso(uwi)	0.0020	6 49	22.24	A3401111/1111	unio/mir/mg	24.01	A3401111/11111	7 92	24.66
1 0.0097 21.66 Km 0.00144 20.99 Km 0.0137 20.58 Km 1.5 0.0125 27.91 0.61 0.0124 22.814 0.61 0.0130 22.03 0.0130 22.03 0.0150 33.34 1.5 0.0144 32.38 0.0144 32.38 0.0150 33.44 2.5 0.0144 32.38 0.0155 34.61 0.0152 35.94 2.60 0.0144 32.38 0.0155 34.61 0.0152 35.94 2.60 0.0044 32.38 0.0155 34.61 0.0052 17.2 Km 2.5 0.0017 22.66 2.70 0.0004 8.46 7.0 0.0052 Km 0.0052 Km 0.0052 Km 0.0052 Km 0.0052 Km 0.0052 1.52 Km 0.0052 1.52 Km 0.0052 5.52 2.53 0.0122 2.54 0.0122 2.54 0.0122 2.54 1.5	0.25	0.0072	16.08	33.34	0.0025	16.75	54.01	0.0085	18.98	34.30
2.5 0.0128 22.14 0.61 0.0124 27.69 0.67 0.0124 27.69 0.43 10 0.0144 32.15 0.0145 32.38 0.0152 33.34 25 0.0144 32.15 0.0155 34.61 0.0155 34.61 0.0165 3.0144 32.38 0.0155 34.61 0.0025 53.94 255 0.0144 22.58 0.0145 32.38 0.0155 34.61 0.25 0.0014 2.96 0.0002 4.65 27.04 0.00025 52.74 6.00025 52.74 6.00026 13.12 7.67 Km 0.50 0.0107 22.63 0.88 0.0090 23.06 0.0105 22.51 0.0122 25.81 0.0122 25.81 0.0152 2.84 0.0155 3.84 15 0.0120 25.39 0.0122 25.81 0.0122 25.81 0.0155 2.84 15 0.0117 22.63 0.0122 25	1	0.0097	21.66	Km	0.0094	20.99	Km	0.0137	30.59	Km
5 0.0125 27.91 0.0128 28.14 0.0130 20.03 15 0.0144 32.15 0.0144 32.38 0.0150 33.34 15 0.0146 32.38 0.0144 32.38 0.0150 33.49 25 0.0146 32.38 0.0145 32.38 0.0150 33.49 20 0.0146 32.38 0.0145 32.38 0.0152 33.94 4:360(M) A340mmin umoliming Vmax A340mmin umoliming Vmax 0.5 0.0030 6.35 0.0040 8.46 0.0062 13.12 10 0.0117 22.63 0.88 0.0099 20.94 0.83 0.0107 22.81 10 0.0117 24.75 0.0122 25.81 0.0122 25.81 0.0122 25.81 10 0.0120 25.39 0.0122 25.81 0.0122 25.81 0.0122 25.81 10 0.0120 25.39 0.012	2.5	0.0126	28.14	0.61	0.0124	27.69	0.67	0.0124	27.69	0.43
10 0.0144 32.15 0.0152 33.44 15 0.0144 32.38 0.0155 34.41 25 0.0144 32.38 0.0155 34.41 0.0145 32.38 0.0155 34.61 0.0145 32.38 0.0155 34.61 0.25 0.0014 2.96 27.04 0.0022 4.65 0.25 0.0014 2.96 0.0046 8.46 0.0064 17.77 1 0.0084 17.77 Km 0.0080 16.92 Km 0.0064 17.77 1 0.0084 17.77 Km 0.0080 16.92 Km 0.0015 2.25.1 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0125 2.6.41 15 0.0120 2.5.39 0.0122 2.5.81 0.0125 2.6.41 15 0.0120 2.5.39	5	0.0125	27.91		0.0126	28.14		0.0130	29.03	
15 0.0146 32.38 0.0144 32.15 0.0150 33.481 25 0.0144 32.15 0.0145 32.38 0.0155 34.61 2600H 0131X #1 #2 #3 0.0155 34.61 0.0152 33.94 4.460(M) A3400mmin umoliming Vmax A3400mmin umoliming Vmax A3400mmin umoliming Vmax 0.5 0.0030 6.35 0.0040 8.46 0.0062 13.12 Vmax A3400mmin umoliming Vmax A3400mmin umoliming Vmax A3400mmin 0.0162 2.25.81 0.0172 2.25.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 2.5.81 0.0122 </td <td>10</td> <td>0.0144</td> <td>32.15</td> <td></td> <td>0.0145</td> <td>32.38</td> <td></td> <td>0.0152</td> <td>33.94</td> <td></td>	10	0.0144	32.15		0.0145	32.38		0.0152	33.94	
<td>15</td> <td>0.0145</td> <td>32.38</td> <td></td> <td>0.0144</td> <td>32.15</td> <td></td> <td>0.0150</td> <td>33.49</td> <td></td>	15	0.0145	32.38		0.0144	32.15		0.0150	33.49	
1. 1	25	0.0144	32.15		0.0145	32.38		0.0155	34.61 33.94	
242GH 131X #1 *7 #3 d=iso(M) Advommin Valominim	50	0.0140	02.00		0.0100	04.01		0.0102	00.04	
d-Bac(M) A340mm/min umal/mining Vmax A340mm/min	D2HGDH G131X	#1			#2			#3		
u.2.5 0.0014 2.96 27.04 0.0022 4.65 27.04 0.0025 5.29 26.72 1 0.0084 17.77 Km 0.0080 18.92 Km 0.0084 17.77 Km 2.5 0.0107 22.63 0.88 0.0199 22.04 0.0105 22.81 0.0105 22.81 0.0125 22.81 0.0125 22.81 0.0125 22.81 0.0125 25.81 0.0125 25.81 0.0125 25.64 250 0.0122 25.81 0.0121 25.60 0.0125 25.64 25.64 2HODH A20T #1 #2 #3 0.0125 25.64 25.53 27.75 0.0025 5.38 27.64 0.5 0.0020 D.50 27.5 0.0012 25.83 0.0112 26.64 2HODH A20T #1 #2 #3 0.025 1.3.8 Km 0.0055 1.3.8 Km 0.0055 1.3.8 Km 0.0056 1.3.8	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax
U.S. U.U.SU 6.35 Kn 0.0080 8.46 0.0082 117.77 Kn 1 0.0084 17.77 Kn 0.0085 0.0080 0.33 0.0107 22.63 0.5 1 0.01017 22.63 0.0107 22.64 0.0117 22.65 0.0107 22.65 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0122 25.61 0.0125 26.44 2400H A0001 11 mmolinitim Vmax A340mminim unolminitim Vmax A340minitim 0.0022 5.53 27.45 0.025 0.0000 5.02 27.5 0.0018 4.52 0.0007 17.54 Kn 0.25 0.0040 10.05 Kn 0.0005 13.82 Kn 0.0007 17.54 Kn 1 0.0040 10.51 Kn 0.0016 26.33 0.0111	0.25	0.0014	2.96	27.04	0.0022	4.65	27.04	0.0025	5.29	26.72
1. Location 11.1.1 Pain Location 10.25 Cuil Location Location <thlocation< th=""> Location Location</thlocation<>	0.5	0.0030	6.35	Km	0.0040	8.46	Km	0.0062	13.12	Km
1 0.0107 22.83 0.00 0.0105 22.81 0.0105 22.81 15 0.0120 25.39 0.0122 25.81 0.0122 25.81 25 0.0120 25.39 0.0122 25.81 0.0125 25.81 26 0.0120 25.39 0.0122 25.81 0.0125 26.44 2400H A200T #1 wslave A340mm/min unolimis/mg Vmax A340mm/min unolimis/mg Vmax A340mm/min 0.0022 5.53 27.45 0.0024 5.53 27.45 0.50 0.0020 5.02 27.5 0.0018 4.52 0.0077 10.34 Kmax 6.4340mm/min 0.0025 1.53 Kmax 6.53 0.0111 27.84 0.68 0.0111 27.85 0.0077 10.34 Kmax 6.53 0.0111 27.84 0.0107 10.32 Kmax 6.53 0.0111 27.84 0.0166 26.83 0.0110 25.83 0.0116 2.84 0.0166 <td>26</td> <td>0.0084</td> <td>22.62</td> <td>0.99</td> <td>0.0080</td> <td>20.04</td> <td>0.92</td> <td>0.0084</td> <td>22.62</td> <td>0.6</td>	26	0.0084	22.62	0.99	0.0080	20.04	0.92	0.0084	22.62	0.6
10 0.0117 24.75 0.0122 25.81 0.0122 25.81 0.0122 25.81 25 0.0122 25.81 0.0120 25.81 0.0121 25.61 260012 25.81 0.0122 25.81 0.0122 25.81 0.0123 25.81 240074 200 71 70 </td <td>2.5</td> <td>0.0107</td> <td>22.63</td> <td>0.00</td> <td>0.0109</td> <td>23.06</td> <td>0.05</td> <td>0.0105</td> <td>22.03</td> <td>0.0</td>	2.5	0.0107	22.63	0.00	0.0109	23.06	0.05	0.0105	22.03	0.0
15 0.0120 25.39 0.0122 25.81 0.0122 25.81 0.0122 25.81 0.0122 25.81 0.0122 25.81 0.0122 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0125 25.81 0.0026 5.02 27.5 0.0018 4.52 7.75 0.0018 4.52 7.75 0.0018 4.52 0.0007 13.34 0.83 0.0077 13.34 0.63 0.0077 13.34 0.63 0.0111 27.5 0.0106 26.33 0.0111 27.85 0.0111 27.85 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33 0.0106 26.33	10	0.0117	24.75		0.0122	25.81		0.0122	25.81	
25 0.0122 25.81 0.0120 25.39 0.0121 25.61 2HGDH A208T #1 #2 #3 Addomminin unodimixing Vmax Addominin unodimixing Vmax Addominin <t< td=""><td>15</td><td>0.0120</td><td>25.39</td><td></td><td>0.0122</td><td>25.81</td><td></td><td>0.0122</td><td>25.81</td><td></td></t<>	15	0.0120	25.39		0.0122	25.81		0.0122	25.81	
50 0.0120 25.39 0.0122 25.81 0.0125 28.44 2HODH A200T #1 #2 #3 4.340mminin umalinining Vmax A340mminin umalinining Vmax A340mininin umalinining Vmax <td< td=""><td>25</td><td>0.0122</td><td>25.81</td><td></td><td>0.0120</td><td>25.39</td><td></td><td>0.0121</td><td>25.60</td><td></td></td<>	25	0.0122	25.81		0.0120	25.39		0.0121	25.60	
2HODH A280T F1 F2 F3 0.25 0.0000 5.02 27.5 0.0018 undifficient of the second sec	50	0.0120	25.39		0.0122	25.81		0.0125	26.44	
d-acir.Min A340mm/min umol/min/min	D2HGDH A208T	#1			#2			#3		
0.025 0.0020 0.0022 0.0023 0.0010 25.83 0.00101 25.83 0.01101 27.88 15 0.0110 25.812 0.0105 25.33 0.0100 25.12 0.0105 25.83 0.0100 25.12 21000H 22.91 1 0.0105 25.83 0.0106 25.12 0.0106 25.12 2400H 21.71 0.025 0.018 27.13 0.0105 28.89 0.0102 24.52 26.5 0.0102 24.52 26.5 0.0165 28.94 0.0114 2.62 29.6 0.01014 26.24 26.6	d-iso(uM)	#1 4340nm/min	umol/min/ma	Vmax	#2 4340nm/min	umol/min/ma	Vmax	#3 4340nm/min	umol/min/ma	Vmax
0.5 0.0040 10.05 0.0055 13.82 Km 1 0.0058 11.57 Km 0.0065 13.82 Km 2.5 0.0071 17.84 0.88 0.0073 18.34 0.87 0.0077 19.34 0.63 10 0.0100 25.12 0.0106 26.63 0.0111 27.88 0.63 25 0.0101 25.12 0.0106 26.63 0.0116 26.83 25 0.0100 25.12 0.0106 26.83 0.0106 26.83 25 0.0100 25.12 0.0106 26.83 0.0106 26.83 2600 0.0107 13.36 3.36 0.0025 4.67 29.44 A340m/min unce/min/mg Vmax 0.25 0.0018 3.36 0.0058 17.95 Km 0.0058 10.122 29.42 0.0114 14.44 Km 0.25 0.0128 25.80 0.0152 28.42 0.0155 28.98	0.25	0.0020	5.02	27.5	0.0018	4.52	27.59	0.0022	5.53	27.45
1 0.0058 14.57 Km 0.0070 17.58 Km 2.5 0.0071 17.84 0.8 0.0073 15.83 0.070 17.58 0.63 5 0.0062 23.11 0.0900 22.61 0.0103 25.81 0.0113 27.83 10 0.0100 25.12 0.0106 25.33 0.0100 25.13 25.33 0.0100 25.13 25.33 0.0100 25.13 25.33 0.0100 25.13 25.33 0.0100 25.13 25.33 0.0105 25.33 0.0105 25.33 25.13 25.33 0.0105 25.33 0.0105 25.33 0.0105 25.33 0.0106 27.13 0.0105 25.34 0.0114 2.62 29.6 0.5 0.0068 12.74 0.006 17.95 Km 0.0079 14.77 0.0114 2.62 2.93 0.0113 2.240 0.0114 2.62 2.63 0.0155 2.840 0.0155 2.840 0.0155 2.840	0.5	0.0040	10.05		0.0045	11.30		0.0055	13.82	
2.5 0.0071 17.84 0.98 0.0073 18.34 0.87 0.0077 19.34 0.63 10 0.0090 25.12 0.0096 26.63 0.0111 27.88 0.0105 25.33 0.0106 25.12 25 0.0100 25.12 0.0105 25.38 0.0106 28.53 0.0106 28.53 25 0.0100 25.12 0.0105 25.38 0.0106 28.58 25.38 240GH E22W #1 #2 #3 430mr/min uncliminia Umax A340mr/min uncliminia Umax A340mr/min uncliminia Umax A340mr/min Umax A340mr/min Umax 1.00066 17.95 Km 0.0058 10.64 0.0079 14.74 Km 1 0.0056 17.95 Km 0.0058 10.0152 22.99 0.073 22.43 0.0152 22.42 0.0151 22.84 0.0152 28.42 0.0155 28.64 0.0155 28.64 0.0155	1	0.0058	14.57	Km	0.0063	15.83	Km	0.0070	17.58	Km
5 0.0062 23.11 0.0060 22.61 0.0163 25.87 10 0.0160 25.12 0.0165 25.63 0.0161 27.88 10 0.0110 27.89 0.0165 25.33 0.0105 25.13 25 0.0107 26.88 0.0168 27.13 0.0105 26.38 2HODH R21W #1 #2 #3 4.0108 27.13 0.0105 26.38 2HODH R21W #1 #2 #3 0.0105 26.38 0.0105 26.39 2HODH R21W #1 #2 #3 0.0016 27.13 0.0016 22.52 29.6 0.5 0.0068 12.71 0.0068 10.84 0.0017 2.82 29.6 0.0113 2.22 2.91 0.0113 2.23 2.23 0.0113 2.240 0.0114 2.82 0.07 0.0123 2.240 0.0114 2.82 0.0155 2.818 0.0155 2.818 0.0155 2.818 0.0155	2.5	0.0071	17.84	0.98	0.0073	18.34	0.87	0.0077	19.34	0.63
10 0.0110 25.12 0.0106 228.53 0.0111 22.13 20 0.0107 25.12 0.0105 25.38 0.0105 25.13 20 0.0107 25.12 0.0105 25.38 0.0105 26.38 240GH 822W #1 #2 #3 4300m/min unclimiting Vmax 0-50000 0.0068 3.36 300.5 0.0025 4.67 29.94 A300m/min unclimiting Vmax 0.55 0.0068 17.95 Km 0.0058 10.84 0.0079 14.77 1 0.0066 17.95 Km 0.0068 17.95 0.0130 24.99 0.7 5 0.0116 28.98 0.0155 28.42 0.0151 28.42 15 0.0155 28.98 0.0155 28.42 0.0155 28.42 26 0.0155 28.94 0.0155 28.42 0.0155 28.42 26 0.0156 28.42 0.0015 </td <td>5</td> <td>0.0092</td> <td>23.11</td> <td></td> <td>0.0090</td> <td>22.61</td> <td></td> <td>0.0103</td> <td>25.87</td> <td></td>	5	0.0092	23.11		0.0090	22.61		0.0103	25.87	
25 0.0100 25.43 0.0106 28.43 25 0.0107 26.89 0.0108 27.13 0.0106 28.43 2HGDH R21W #1 #2 #3 47.3 47.3 47.3 0-isio(M) A340nm/min umal/min/m Vmax A340nm/min umol/min/m Vmax A340nm/min umol/min/m Vmax A340nm/min umol/min/m Vmax A340nm/min umol/min/m Vmax A340nm/min 0.0018 2.2.35 0.0113 2.2.92 2.9.6 0.0113 2.2.93 0.07 0.17.3 2.2.93 0.07 0.0123 2.2.98 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0113 2.2.93 0.0115 2.2.93 0.0115 2.2.93 0.0115 2.2.93 0.0115 2.2.93 0.0112	10	0.0100	25.12		0.0106	26.63		0.0111	27.88	
50 0.0107 26.88 0.0108 27.13 0.0105 28.38 2HODH F22W #1 #2 #3 *3 *4	15	0.0100	27.00		0.0105	26.38		0.0100	25.12	
Children R212W #1 #2 #3 #3 d-liso(JM) A340mm/min umol/min/min Vmax A340mm/min	50	0.0107	26.88		0.0108	27.13		0.0105	26.38	
2HGDR R212W #1 #2 #3 d-iso(M) A3400m/min umol/min/mg Vmax A340m/min umol/min/mg Vmax A3400m/min umol/min/mg Vmax A340m/min umol/min/mg Vmax A340m/min/min umol/min/mg Vmax A340m/min/mg umol/min/mg Vmax A340m/min/min umol/min/mg Vmax A340m/min/m										
d-so(uM) A340ommin umolimium Vinax	D2HGDH R212W	#1			#2			#3		
0.25 0.0018 3.36 3.005 0.0025 4.67 22.94 0.0014 2.45 0.5 0.0066 12.75 K 0.0026 17.85 K 0.0014 2.45 1 0.0066 12.255 K 0.0026 12.85 K 0.0113 22.43 0.0113 22.43 0.0113 24.30 0.7 10 0.0155 28.98 0.0152 28.42 0.0151 28.38 0.0152 28.42 0.0151 28.38 25 0.0150 28.04 0.0156 28.16 0.0154 28.79 28.89 240DH R421H #1 #2 #3 4.36(mm/min umolimis/mg Vmax A34(mm/min umolimis/mg Vmax A4.42 25.16 0.0154 28.39 20.25 28.50 0.0201 1.2.2 0.0205 4.2.2 25.14 0.0204 4.2.2 25.16 0.0204 4.2.2 25.16 0.0204 4.2.2 25.16 0.0205 2.0.2.1 2.0.2 </td <td>d-iso(uM)</td> <td>A340nm/min</td> <td>umol/min/mg</td> <td>Vmax</td> <td>A340nm/min</td> <td>umol/min/mg</td> <td>Vmax</td> <td>A340nm/min</td> <td>umol/min/mg</td> <td>Vmax</td>	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax
0.0 0.0006 1.2.95 Km 0.0006 10.4.4 Km 1.5 0.0106 1.2.95 0.0123 22.98 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.99 0.0173 22.93 0.0173 22.93 0.0173 22.83 0.0175 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 22.84.2 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0155 2.8.98 0.0115 2.8.77 0.0055 5.02 5.02 5.02 5.02 5.02 5.02 5.02 5.02 5.02 2.5.12 <td< td=""><td>0.25</td><td>0.0018</td><td>3.36</td><td>30.05</td><td>0.0025</td><td>4.67</td><td>29.94</td><td>0.0014</td><td>2.62</td><td>29.6</td></td<>	0.25	0.0018	3.36	30.05	0.0025	4.67	29.94	0.0014	2.62	29.6
2.5 0.0128 2.2455 0.0723 2.299 0.87 0.0123 2.299 0.77 5 0.0138 2.2580 0.0120 22.43 0.0130 24.30 24.30 10 0.0155 28.98 0.0152 28.42 0.0151 28.38 25 0.0150 28.04 0.0156 28.98 0.0154 28.79 25 0.0150 28.04 0.0155 29.16 0.0154 28.79 2460DR R421H #1 #2 #3 A340mm/min Umax A340mm/min umol/min/min 0.0155 28.16 0.0154 28.79 2460DR R421H #1 #2 #2 0.0155 20.16 0.0058 10.48 28.35 0.5 0.0060 15.08 Km 0.0068 16.86 Km 0.0071 12.29 0.68 0.0111 22.31 0.0111 22.31 0.68 5 0.0111 22.31 0.68 5 0.0111 22.31 0.68 0	0.5	0.0006	17.95	Km	0.0000	17.95	Km	0.0073	19.77	Km
5 0.0138 25.80 0.0120 22.43 0.0130 24.30 10 0.0155 28.89 0.0152 28.42 0.0151 28.33 15 0.0155 28.89 0.0155 28.98 0.0152 28.42 25 0.0150 28.64 0.0155 29.16 0.0155 28.98 201010 28.64 0.0155 29.16 0.0155 28.98 2400H 421H 11 72 73 0.0055 29.16 0.0155 29.98 2400H 421H 11 72 70 0.0052 50 50 50 20.58 50 0.0052 10.45 70 20.0052 10.45 70 20.058 10.45 70 20.058 10.45 70 20.058 10.45 70 22.31 10.111 22.31 10.111 22.31 10.111 22.31 10.111 22.31 10.111 22.31 10.112 23.12 10.112 23.12 10.112 23.11	2.5	0.0126	23.55	0.79	0.0123	22.99	0.87	0.0123	22.99	0.7
10 0.0155 28.98 0.0152 28.42 0.0151 28.24 25 0.0150 28.04 0.0155 29.86 0.0154 28.42 25 0.0150 28.04 0.0155 29.16 0.0154 28.98 2460H R421H #1 #2 #2 0.0155 29.16 0.0154 28.98 2460H R421H #1 #1 #2 #2 A340mmbin umol/mining Vmax A340mmbin umol/mining 26.35 0.0000 15.08 Km 0.00091 13.67 0.008 19.68 Km 1 0.0000 15.08 Km 0.00091 13.29 0.68 0.0111 22.31 0.0111 23.10 0.68	5	0.0138	25.80		0.0120	22.43		0.0130	24.30	
15 0.0152 28.98 0.0155 28.98 0.0152 28.44 0.0155 28.98 0.0152 28.79 250 0.0150 28.64 0.0155 29.16 0.0155 28.98 0.0155 28.98 2450DH 421H #1 #28.04 0.0156 29.16 0.0155 28.98 2460DH 421H #1 #28.04 0.0007 28.93 7.0007 28.93 0.50 0.0000 14.02 28.04 0.0024 44.22 27.4 0.0025 1.05 5.02 28.35 0.5 0.0060 12.06 0.0091 18.29 Km 0.068 18.99 Km 2.5 0.0097 19.49 0.74 0.0096 19.29 0.58 0.0011 22.31 0.111 22.31 0.112 22.31 0.0112 22.31 0.0125 25.12 0.0126 25.32 0.0126 25.32 0.0126 25.32 0.0126 25.32 0.0126 25.32 0.0126 25.32 </td <td>10</td> <td>0.0155</td> <td>28.98</td> <td></td> <td>0.0152</td> <td>28.42</td> <td></td> <td>0.0151</td> <td>28.23</td> <td></td>	10	0.0155	28.98		0.0152	28.42		0.0151	28.23	
25 0.0150 28.04 0.0155 29.16 0.0154 28.79 2HGDH R421H F1 52 53 53 53 53 53 53 53 53 53 53 53 53 55 53 53 53 53 55 53 53 55 53 55 56 50,000 10.26 0.0026 10.45 74 53 55 50,000 10.26 0.0026 10.45 74 55 50,000 10.26 0.0008 19.69 Km 0.0088 19.69 Km 0.0088 19.69 Km 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0125 25.12 0.0126 25.12 0.0126 25.32 21.21 0.0126 25.12 0.0126 26.13<	15	0.0155	28.98		0.0155	28.98		0.0152	28.42	
Bit Bit <td>25</td> <td>0.0150</td> <td>28.04</td> <td></td> <td>0.0156</td> <td>29.16</td> <td></td> <td>0.0154</td> <td>28.79</td> <td></td>	25	0.0150	28.04		0.0156	29.16		0.0154	28.79	
2H2GH R421H #1 #2 #3 04:bic(M) A340mm/min umod/min/min/min/min/min/min/min/min/min/min	50	0.0100	20.00		0.0100	20.10		0.0100	20.00	
d-iso(M) A340nm/min umol/min/min Umax A340nm/min umol/min/min umol/min/min <th< td=""><td>D2HGDH R421H</td><td>#1</td><td></td><td></td><td>#2</td><td></td><td></td><td>#3</td><td></td><td></td></th<>	D2HGDH R421H	#1			#2			#3		
u.z.b 0.0020 4.02 28.24 0.0022 4.42 25,74 0.0025 5.02 26.35 0.5 0.0660 112.068 0.0088 18.67 0.0028 19.45 Km 1 0.0680 16.08 Km 0.0091 18.29 Km 0.0088 19.89 Km 1 0.0011 2.47 0.0025 2.51 0.0013 12.61 0.013 2.51 0.0130 2.61.3 0.0130 2.61.3 0.0125 2.61.3 0.0125 2.61.2 0.0130 2.61.3 0.0125 2.61.2 0.0130 2.61.3 25 0.0126 2.51.2 0.0125 2.61.2 0.0126 2.61.2 2.51.2 0.0130 2.61.3 25 0.0126 2.51.2 0.0125 2.63.2 2.62.2 0.0125 2.61.2 0.0130 2.61.3 200404 0.4020 1.66.8 0.0021 5.63 2.03.6 0.0015 4.02 3.06 0.5 0.0025	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax
J. J. UJONO 12.50 UJONO 13.67 UJONO 11.86 UJONO 11.86 UJONO 11.86 Km 1 0.0080 11.64 0.74 0.00111 12.23 0.0111 12.83 Km 2.0 0.0111 12.31 0.0111 22.31 0.01111 22.31 0.01111 22.31 0.01111 22.31 0.01111 22.31 0.01111 22.31 0.01125 25.12 0.0125 25.12 0.0125 25.12 0.0126 25.22 2HOH ALST 1 50 0.0125 25.12 0.0126 25.23 24001 26.63 20.0126 25.12 0.0126 25.32 2HOH ALST 1 50 0.0025 25.12 0.0126 25.32 2400 20.66 20.0126 25.32 2HOH ALST 1 50 0.0025 25.12 0.0126 25.32 20.66 0.0156 40.20 30.66 0.55 0.0051 16.88 0.00051 11.25	0.25	0.0020	4.02	26.24	0.0022	4.42	25.74	0.0025	5.02	26.35
2.5 0.0007 118.40 num 119.20 num 118.20 0.88 5 0.0011 22.31 0.0111 22.31 0.0111 22.31 0.081 10 0.01123 24.72 0.0125 25.32 0.0110 26.13 25 0.0126 25.32 0.0125 25.12 0.0125 25.32 25 0.0126 25.32 0.0125 25.12 0.0126 25.32 2400H A25T #1 #2 #3 4.340mm/min umol/min/min umol/min/min 0/max 4-0.0(M) A3400mm/min umol/min/min Vmax A340mm/min umol/min/min umol/min/min 0/max 4.00 30.66 0.5 0.0063 16.88 0.0042 11.25 0.0048 12.80 30.51 1 0.0073 19.56 Km 0.0069 24.12 0.72 0.0087 23.31 0.46 0.0959 24.12 0.0015 38.14 2.5 0.0068 26.25	0.5	0.0060	12.06	Km	0.0068	13.67	Km	0.0052	10.45	Km
5 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0111 22.31 0.0112 24.13 0.0125 25.12 0.0125 25.12 0.0125 25.12 0.0125 25.12 0.0126 25.32 250 0.0126 25.12 0.0126 25.22 0.0126 25.32 2HGDH ALST ft 7 27.80 0.0126 25.32 0.0126 25.32 2HGDH ALST ft 8 0.0021 5.63 20.60 4.02 30.66 0.55 0.0025 7.07 27.84 0.0021 17.65 0.0048 12.80 0.0048 12.80 0.0048 12.80 0.0048 12.80 0.0048 12.80 0.0048 12.80 0.0048 12.80 0.0049 2.81.41 0.69 2.81.41 0.69 2.81.41 0.69 2.81.41 0.69 2.81.41 0.69 2.81.41 0.69 2.81.41 0.69 2.81.41	25	0.0097	19.49	0.74	0.0096	19.29	0.58	0.0091	18.29	0.68
10 0.0123 24.72 0.0126 25.32 0.0130 26.13 15 0.0130 26.13 0.0125 25.12 0.0130 26.13 25 0.0126 25.32 0.0125 25.12 0.0130 26.13 0.0125 25.12 0.0126 25.32 0.0125 25.32 2HGDH A425T #1 #2 #3 4.340mm/min umol/min/min Umol/min/min/min/min/min/min Umol/min/min/min/min/min/min/min/min/min/min	5	0.0111	22.31		0.0111	22.31		0.0111	22.31	
15 0.0130 26.13 0.0125 25.12 0.0125 25.12 25 0.0126 25.12 0.0126 26.13 60 0.0125 25.12 0.0126 25.12 2500H AL35T 1 50 0.0126 25.12 4-lso(M) A340ommin umol/min/min umol/min/min umol/min/min 0.05 0.0025 5.07 27.84 0.0024 5.63 20.36 0.0114 20.0025 6.0014 20.0025 6.0014 20.0025 1.00073 11.25 0.0048 12.26 0.0048 12.80 1.0014 1.059 1.059 1.059 0.0104 2.0512 0.0107 21.17 Km 2.5 0.0067 23.31 0.46 0.0090 24.12 0.72 0.0067 23.14 0.69 10 0.0069 26.53 0.0101 27.64 0.0114 30.55 2.5 0.0069 26.53 0.0101 27.64 0.0111 29.74 0.0111	10	0.0123	24.72		0.0126	25.32		0.0130	26.13	
zp 0.0120 25.32 0.0125 25.12 0.0130 26.13 d4so(M) 0.0125 25.12 0.0124 24.92 0.0126 25.32 2HGDH A426T #1 #2 #2 m3 3 3 0.55 0.0025 6.70 27.88 0.0021 5.63 29.36 0.0015 4.02 30.66 0.5 0.0025 6.70 27.88 0.0021 5.63 29.36 0.0015 4.02 30.66 0.5 0.0067 12.31 0.46 0.0062 11.25 0.0048 12.49 Km 0.0015 28.14 0.069 25.11 0.008 22.12 0.72 0.0105 28.14 0.69 5.5 0.0105 28.14 0.0105 28.14 0.0105 28.14 0.0105 28.40 50 0.0099 26.53 0.0098 26.26 0.0106 28.40 255 0.0099 26.53 0.0098 26.26 0.0105 28.14	15	0.0130	26.13		0.0125	25.12		0.0125	25.12	
No. Control EASLE CONTROL Contro <thcontro< th=""> Contro</thcontro<>	25	0.0126	25.32		0.0125	25.12		0.0130	26.13	
2H2GD Ad25T #1 #2 #3 d-isio(M) Ad40mmin umol/min/mg Vmax A340m/min/min/mg Vmax A340m/min/mg Vmax A340m/min/min/mg Vmax A340m/min/mg	50	0.0125	23.12		0.0124	24.02		0.0120	20.02	
d-iso(M) A340nm/min umol/min/min	D2HGDH A426T	#1			#2			#3		
0.25 0.0025 6.70 27.88 0.0021 5.63 20.36 0.0015 4.02 30.66 0.5 0.0063 16.88 0.0042 11.25 0.0048 12.86 12.86 1 0.0073 19.56 Km 0.0068 17.68 Km 0.0079 21.17 Km 2.5 0.0084 24.12 0.72 0.0087 23.31 0.69 5 0.0098 26.26 0.0100 28.80 0.0105 28.14 10 0.0099 26.53 0.0111 29.74 0.0105 28.14 25 0.0109 26.53 0.0111 29.74 0.0105 28.14 25 0.0099 26.53 0.0098 26.26 0.0106 28.40 50 0.0099 26.53 0.0098 26.26 0.0106 28.40	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax
u.5 UUM-5 16.88 U.0042 11.25 U.0048 12.86 1 0.0073 19.55 Km 0.0066 17.88 Km 0.0077 21.17 Km 2.5 0.0689 23.31 0.46 0.0080 24.12 0.72 0.0097 23.14 0.69 1 0.0099 26.53 0.0100 26.6 0.0101 20.54 15 0.0099 26.53 0.0111 22.74 0.0105 28.14 25 0.0105 28.14 0.0105 28.14 50 0.0099 26.53 0.0098 26.26 0.0106 28.40 15 0.0099 26.53 0.0098 26.26 0.0106 28.40 15 0.0099 26.53 0.0098 26.26 0.0106 28.40	0.25	0.0025	6.70	27.88	0.0021	5.63	29.36	0.0015	4.02	30.66
1 0.0009 21.1 0.01 0.0009 21.1 0.01 2.5 0.0087 23.31 0.46 0.0090 24.12 0.72 0.0097 23.31 0.69 5 0.0098 26.26 0.0100 28.80 0.0105 28.14 0.055 15 0.0099 26.53 0.0111 29.74 0.0105 28.14 25 0.0109 26.53 0.0112 29.74 0.0105 28.14 50 0.0099 26.53 0.0098 26.26 0.0106 28.40	0.5	0.0063	16.88	Km	0.0042	11.25	Km	0.0048	12.86	Km
5 0.0098 28:28 0.0100 26:80 0.0105 28:14 10 0.0099 26:53 0.0111 27:06 0.0105 28:14 15 0.0099 26:53 0.0111 29:74 0.0105 28:14 25 0.0105 28:14 0.0105 28:14 0.0115 28:14 50 0.0099 26:53 0.0098 26:26 0.0106 28:40	25	0.0073	23.31	0.46	0.0000	24.12	0.72	0.0079	23.31	0.69
10 0.0099 26.53 0.0101 27.06 0.0114 30.65 15 0.0099 26.53 0.0111 29.74 0.0105 28.14 25 0.0105 28.14 0.0105 28.14 0.0115 29.74 50 0.0099 26.53 0.0098 26.26 0.0106 28.40 regree kinectis calculated using the Michaelis-Menten equation	2.5	0.0098	26.26	0.40	0.0100	26.80	0.72	0.0105	28.14	0.00
15 0.009 26.53 0.0111 29.74 0.0105 28.14 25 0.0105 28.14 0.0105 28.14 0.0115 29.74 50 0.0099 26.53 0.0098 26.26 0.0106 28.40	10	0.0099	26.53		0.0101	27.06		0.0114	30.55	
25 0.0105 28.14 0.0105 28.14 0.0111 29.74 50 0.0099 26.53 0.0098 26.26 0.0106 28.40 nzyme kinectis calculated using the Michaelis-Menten equation	15	0.0099	26.53		0.0111	29.74		0.0105	28.14	
su u.uuse 26.53 0.0098 26.25 0.0106 28.40	25	0.0105	28.14		0.0105	28.14		0.0111	29.74	
nzyme kinectis calculated using the Michaelis-Menten equation	50	0.0099	26.53		0.0098	26.26		0.0106	28.40	
nzyme kinectis calculated using the Michaelis-Menten equation										
	Enzyme kinectis ca	alculated using	g the Michaelis	Menten	equation					

	Transient	Transfection								
MSCV (0.5L	ig)	#1			#2			#3		
	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	
	0.25	0.0012	4.95	32.56	0.0012	4.95	31.8	0.0013	5.36	Vmax
	0.5	0.0026	10.72		0.0027	11.13		0.0026	10.72	30.89
	1	0.0032	13.19	Km	0.0035	14.43	Km	0.0036	14.84	
	2.5	0.0041	16.90	1.51	0.0041	16.90	1.34	0.0043	17.73	Km
	5	0.0060	24.73		0.0060	24.73		0.0065	26.80	1.13
	10	0.0073	30.09	protein	0.0072	29.68	protein	0.0074	30.51	
	15	0.0074	30.51	39ug	0.0073	30.09	39ug	0.0070	28.86	protein
	25	0.0075	30.92	-	0.0074	30.51	-	0.0070	28.86	39ug
	50	0.0074	30.51		0.0073	30.09		0.0070	28.86	
D2HGDH W	T(0.5ug)	#1			#2			#3		
	d-iso(uM)	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	Vmax	A340nm/min	umol/min/mg	
	0.25	0.0013	5.23	33.58	0.0013	5.23	33.71	0.0014	5.63	Vmax
	0.5	0.0031	12.46		0.0032	12.86		0.0031	12.46	33.43
	1	0.0040	16.08	Km	0.0042	16.88	Km	0.0045	18.09	
	25	0.0058	23.31	1.02	0.0058	23.31	0.96	0.0059	23.71	Km
	5	0.0071	28.54		0.0075	30.14		0.0075	30.14	0.9
	10	0.0077	30.95	nrotein	0.0076	30.55	protein	0.0075	30.14	0.0
	15	0.0079	31 75	4000	0.0078	31.35	4000	0.0079	31 75	protein
	26	0.0091	22.56	Houg	0.0092	22.06	Houg	0.0070	21.76	4000
	20	0.0070	21.75		0.0082	32.50		0.0073	32.66	Houg
	50	0.0075	51.75		0.0000	32.15		0.0001	32.30	
MSCV/0 75		#1			#2			#2		
11130 4(0.75	d in (1.11.11)	#1 A240mm/min		Veen	#2 A 2 40 mm/min		Vmeu	#J	um al (min (m a	
	u-iso(uwi)	A3400000	unio/min/mg	24.07	A3401111/11111	unormining 4.52	24.66	A3401111/11111	uno/min/mg	1/100.000
	0.25	0.0012	4.95	31.07	0.0011	4.55	31.00	0.0012	4.95	VIIIax
	0.5	0.0026	10.72		0.0026	10.72		0.0025	10.31	31.09
	1	0.0033	13.60	ĸm	0.0032	13.19	Km	0.0035	14.43	
	2.5	0.0042	17.31	1.37	0.0042	17.31	1.36	0.0045	18.55	Km
	5	0.0060	24.73		0.0063	25.97		0.0060	24.73	1.22
	10	0.0074	30.51	Protein	0.0073	30.09	protein	0.0072	29.68	
	15	0.0073	30.09	39ug	0.0072	29.68	39ug	0.0072	29.68	protein
	25	0.0073	30.09		0.0070	28.86		0.0071	29.27	39ug
	50	0.0072	29.68		0.0073	30.09		0.0071	29.27	
	50	0.0072	29.68		0.0073	30.09		0.0071	29.27	
D2HGDH W	50 T(0.75ug)	0.0072 #1	29.68		0.0073 #2	30.09		0.0071 #3	29.27	
D2HGDH W	50 T(0.75ug) d-iso(uM)	0.0072 #1 A340nm/min	29.68 umol/min/mg	Vmax	0.0073 #2 A340nm/min	30.09 umol/min/mg	Vmax	0.0071 #3 A340nm/min	29.27 umol/min/mg	
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25	0.0072 #1 A340nm/min 0.0015	29.68 umol/min/mg 5.36	Vmax 36.83	0.0073 #2 A340nm/min 0.0015	30.09 umol/min/mg 5.36	Vmax 36.28	0.0071 #3 A340nm/min 0.0016	29.27 umol/min/mg 5.72	Vmax
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5	0.0072 #1 A340nm/min 0.0015 0.0033	29.68 umol/min/mg 5.36 11.79	Vmax 36.83	0.0073 #2 A340nm/min 0.0015 0.0035	30.09 umol/min/mg 5.36 12.50	Vmax 36.28	0.0071 #3 A340nm/min 0.0016 0.0038	29.27 umol/min/mg 5.72 13.58	Vmax 36.24
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047	29.68 umol/min/mg 5.36 11.79 16.79	Vmax 36.83 Km	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049	30.09 umol/min/mg 5.36 12.50 17.51	Vmax 36.28 Km	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049	29.27 umol/min/mg 5.72 13.58 17.51	Vmax 36.24
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065	29.68 umol/min/mg 5.36 11.79 16.79 23.22	Vmax 36.83 Km 1.243	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064	30.09 umol/min/mg 5.36 12.50 17.51 22.87	Vmax 36.28 Km 1.12	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069	29.27 umol/min/mg 5.72 13.58 17.51 24.65	Vmax 36.24 Km
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22	Vmax 36.83 Km 1.243	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0084	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01	Vmax 36.28 Km 1.12	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37	Vmax 36.24 Km 1.01
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01	Vmax 36.83 Km 1.243 protein	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0084 0.0097	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66	Vmax 36.28 Km 1.12 protein	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0097	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66	Vmax 36.24 Km 1.01
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 28.22 35.01 35.37	Vmax 36.83 Km 1.243 protein 45ug	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0084 0.0097 0.0097	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66	Vmax 36.28 Km 1.12 protein 45ug		29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01	Vmax 36.24 Km 1.01 protein
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37	Vmax 36.83 Km 1.243 protein 45ug	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0084 0.0097 0.0097 0.0096	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.30	Vmax 36.28 Km 1.12 protein 45ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0085 0.0097 0.0098 0.0098	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01	Vmax 36.24 Km 1.01 protein 45ug
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 5 5 5 5 5 5 5 5 5 5 5 5 5	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0099	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 33.94	Vmax 36.83 Km 1.243 protein 45ug	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0084 0.0097 0.0097 0.0096 0.0095	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.30 33.94	Vmax 36.28 Km 1.12 protein 45ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098 0.0098	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23	Vmax 36.24 Km 1.01 protein 45ug
D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.55 10 15 25 50	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 33.94	Vmax 36.83 Km 1.243 protein 45ug	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0084 0.0084 0.0097 0.0097 0.0096	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.66 34.30 33.94	Vmax 36.28 Km 1.12 protein 45ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23	Vmax 36.24 Km 1.01 protein 45ug
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 35.37 33.94	Vmax 36.83 Km 1.243 protein 45ug	0.0073 #2 A340nm/min 0.0015 0.0049 0.0064 0.0084 0.0097 0.0097 0.0095 0.0095 #2	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.30 33.94	Vmax 36.28 Km 1.12 protein 45ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098 0.0098 0.0093 #3	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23	Vmax 36.24 Km 1.01 protein 45ug
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM)	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1 A340nm/min	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 33.94 umol/min/mg	Vmax 36.83 Km 1.243 protein 45ug Vmax	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0097 0.0097 0.0097 0.0095 #2 A340nm/min	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.60 33.94 umol/min/mg	Vmax 36.28 Km 1.12 protein 45ug Vmax	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0065 0.0097 0.0098 0.0098 0.0093 #3 A340nm/min	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23 umol/min/mg	Vmax 36.24 Km 1.01 protein 45ug
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0095 #1 A340nm/min 0.0012	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.37 35.37 35.37 33.94 umol/min/mg 4.95	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0097 0.0097 0.0095 #2 A340nm/min 0.0011	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.30 33.94 umol/min/mg 4.53	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098 0.0098 0.0098 0.0093 #3 A340nm/min 0.0011	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23 umol/min/mg 4.53	Vmax 36.24 Km 1.01 protein 45ug Vmax
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25 0.5	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1 A340nm/min 0.0012 0.0025	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 33.94 umol/min/mg 4.95 10.31	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39	0.0073 #2 A340nm/min 0.0015 0.0049 0.0064 0.0097 0.0097 0.0096 0.0095 #2 A340nm/min 0.0011 0.0025	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.30 33.94 umol/min/mg 4.53 10.31	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82	0.0071 #3 A340nm/min 0.0016 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098 0.0093 #3 A340nm/min 0.0011 0.0026	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23 umol/min/mg 4.53 10.72	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25 0.25 10 0.25 50 15 10 15 15 10 10 15 10 10 15 10 10 15 10 10 10 10 10 10 10 10 10 10	0.0072 #1 A340nm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1 A340nm/min 0.0012 0.0025 0.0032	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 3	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0097 0.0097 0.0095 #2 A340nm/min 0.0011 0.0025 0.0033	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.66 34.30 33.94 umol/min/mg 4.53 10.31 13.60	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0065 0.0097 0.0098 0.0093 #3 A340nm/min 0.0011 0.0026 0.0026	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 35.01 35.01 35.01 35.23 umol/min/mg 4.53 10.72 14.02	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25 50 0.25 0.5 1 2.5 5 1 0 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 1 2.5 1 2.5 1 1 2.5 1 1 2.5 1 1 1 1 1 1 1 1 1 1 1 1 1	0.0072 #1 A340nm/min 0.0013 0.0035 0.0065 0.0098 0.0099 0.0099 0.0099 0.0095 #1 A340nm/min 0.0012 0.0025 0.0032	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 35.37 33.94 umol/min/mg 4.95 10.31 13.19 16.90	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49	0.0073 #2 A340nm/min 0.0015 0.0035 0.0049 0.0064 0.0097 0.0097 0.0096 0.0095 #2 A340nm/min 0.0011 0.0025 0.0033 0.0049	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.66 34.30 33.94 umol/min/mg 4.53 10.31 13.60 20.20	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0097 0.0098 0.0093 #3 A340nm/min 0.0011 0.0026 0.0034 0.0034	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 33.23 umol/min/mg 4.53 10.72 14.02 17.73	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.025 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25 0.5 1 2.5 50 d-iso(uM) 0.25 0.5 1 2.5 5 5 0 1 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 1 2.5 5 0 2.5 5 0 2.5 5 0 5 5 5 0 5 5 5 5 0 5 5 5 5 5 5 5 5 5 5 5 5 5	0.0072 #1 A340mm/min 0.0015 0.0005 0.0079 0.0065 0.0079 0.0099 0.0099 0.0099 0.0099 0.0095 #1 A340nm/min 0.0012 0.0025 0.0022 0.0032	29.68 umol/min/mg 5.36 11.79 23.22 28.22 35.01 35.37 35.37 35.37 33.94 umol/min/mg 4.95 10.31 13.19 16.90 25.15	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49	0.0073 #2 A340mr/min 0.0015 0.0049 0.0064 0.0084 0.0097 0.0096 0.0095 #2 A340mr/min 0.0011 0.0025 0.0033 0.0033 0.0061	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.60 34.60 34.30 33.94 4.53 10.31 13.60 20.20 25.15	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260	0.0071 #3 A340mm/min 0.0016 0.0038 0.0049 0.0065 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 43 A340mm/min 0.0011 0.0024 0.0024 0.0024 0.0034	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23 umol/min/mg 4.53 10.72 14.02 17.73 25.97	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 0.5 10 15 25 50 d-iso(uM) 0.25 0.5 0.5 0.5 15 50 0.5 50 0.5 15 50 0.5 50 0.5 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 15 50 15 50 15 50 15 50 15 50 15 50 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 10 15 50 15 15 50 15 15 50 15 15 50 15 15 15 15 15 15 15 15 15 15	0.0072 #1 4340m/min 0.0015 0.0033 0.0045 0.0079 0.0099 0.0099 0.0095 #1 4340mm/min 0.0015 0.0075 0.0025 0.0025 0.0025 0.0025	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 28.22 25.01 35.37 35.37 35.37 35.37 35.37 35.37 4.95 10.31 13.19 16.90 25.15 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein	0.0073 #2 A340mm/min 0.0015 0.0035 0.0044 0.0084 0.0097 0.0096 0.0095 #2 A340mm/min 0.0095 #2 0.0010 0.0015 0.0025	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.60 33.94 umol/min/mg 4.53 10.31 13.60 30.92	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein	0.0071 #3 A340mm/min 0.0016 0.0038 0.0049 0.0085 0.0098 0.0098 0.0093 #3 A340mm/min 0.0093 #3 A340mm/min 0.0026 0.0026 0.0026	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 33.23 umol/min/mg 4.53 10.72 14.02 14.02 17.73 25.97 29.27	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 5 10 15 5 5 00 0.25 5 0.25 5 00 0.25 1 2.55 1 0.25 5 0 0.25 1 1 2.5 5 1 0.25 5 1 1 2.5 5 1 1 2.5 5 5 1 1 2.5 5 5 5 5 5 5 5 5 5 5 5 5 5	0.0072 #1 A340mm/min 0.0015 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1 A340mm/min 0.0012 0.0022 0.0012 0.0022 0.0012 0.0022	29.68 umol/min/mg 5.56 11.79 16.79 23.22 28.22 35.01 35.37 33.94 umol/min/mg 4.95 10.31 13.19 16.90 25.15 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A340m/015 0.0015 0.0049 0.0064 0.0084 0.0095 #2 A340m/min 0.0095 #2 0.0095 #2 0.0023 0.0023 0.0023 0.0023 0.0061 0.0072	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.30 33.94 umol/min/mg 4.53 10.31 13.60 20.25 15 30.92 25.15 30.92 29.68	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340mm/min 0.0016 0.0049 0.0069 0.0093 0.0093 0.0093 #3 A340mm/min 0.0011 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024	29.27 umol/min/mg 5.72 13.563 17.51 24.65 30.37 34.66 35.01 33.23 umol/min/mg 4.53 10.72 14.02 17.73 25.97 29.27 28.86	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 0.25 0.5 1 2.5 5 0 0.5 15 25 5 0 0 15 25 5 0 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 10 25 5 10 15 25 5 10 15 25 5 10 15 25 5 10 10 25 5 10 10 25 5 10 10 25 5 10 10 12 5 10 15 15 15 15 15 15 15 15 15 15	0.0072 #1 A340mm/min 0.0015 0.0047 0.0065 0.0098 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0012 0.0025 0.0025 0.0025 0.0022 0.0024 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 0.0095 0.0099 0.0099 0.0095 0.0095 0.0099 0.0095 0.0095 0.0095 0.0095 0.0099 0.0095 0.0075 00	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 28.22 23.501 35.37 35.37 33.94 4.95 10.31 13.19 16.90 25.15 30.09 30.092	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A340mm2 0.0015 0.0049 0.0064 0.0084 0.0097 0.0096 0.0096 0.0095 0.0095 #2 A340mm/min 0.0015 0.0025 0.0033 0.0049 0.0061 0.0072 0.0072	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.60 33.94 4.53 10.31 13.60 20.20 25.15 30.92 29.68 28.86	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340mm/min 0.0016 0.0049 0.0069 0.0085 0.0097 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0093 #3 A340mm/min 0.0016 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0026 0.0097 0.0026 0.	29.27 umol/min/mg 5.72 13.56 17.51 24.65 30.37 34.66 35.01 33.23 4.53 10.72 14.02 17.73 17.73 17.73 25.97 29.27 28.86 28.86	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0)	50 T(0.75ug) 0.25 0.5 1 2.5 5 10 15 25 50 0.25 0.5 1 2.5 5 0 0.25 0.5 1 2.5 5 0 0.25 0.5 1 2.5 5 5 0 0.5 5 5 5 5 5 5 5 5 5 5 5 5 5	0.0072 #1 A340mm/0.0015 0.0033 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0092 #1 A340mm/min 0.0012 0.0022 0.0032 0.0021	29.68 umol/min/mg 5.56 11.79 16.79 23.22 28.22 28.22 28.50 16.59 23.53 33.94 umol/min/mg 4.95 10.31 13.19 16.90 25.15 30.09 20.09 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A340m/015 0.0015 0.0049 0.0064 0.0084 0.0097 0.0096 0.0096 0.0096 3.0097 #2 A340m/mini 0.0011 0.0025 #2 A340m/mini 0.0021 0.0023 0.0033 0.0041 0.0021 0.0072	30.09 umol/min/mg 5.56 12.50 17.51 22.87 30.01 34.66 34.66 34.80 33.94 umol/min/mg 4.53 10.31 13.60 20.20 25.15 20.92 29.68 28.86 28.86 30.51	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340mm/min 0.0016 0.0049 0.0069 0.0095 0.0096 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0093 #3 A340mm/min 0.0011 0.0026 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024 0.0024 0.0025 0.00270 0.002700 0.00270000000000	29.27 umol/mir/mg 5.72 13.58 17.51 24.65 36.01 35.01 33.23 umol/min/mg 4.53 10.72 14.02 17.73 25.97 29.27 28.86 28.86 30.09	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0)	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 5 0.25 0.5 1 2.5 5 10 0.25 0.5 1 2.5 5 0 0.25 0.5 1 2.5 5 0 0.25 0.5 1 0.25 5 0.5 1 0.25 5 0.5 1 0.25 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 1 0 0.5 5 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0 0.5 1 0.5 5 0 0 0 5 0 5 0 5 1 0 5 1 0 5 1 0 5 5 0 5 1 0 5 5 1 0 5 5 1 0 5 5 1 1 5 5 1 1 5 5 5 5 5 5 5 5 5 5 5 5 5	0.0072 #1 A340mm/main 0.0015 0.0037 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0025 0.0098 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 0.0025 0.0098 0.0099 0.0099 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0025 0.0098 0.0025 0.0053 0.0053 0.00555 0.00555 0.00555 0.00555 0.00555 0.005555 0.005555 0.0055	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 23.5.01 35.37 35.30 35.37 35.30 35.37 35.30 35.37 35.30	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A3400m15 0.0015 0.0035 0.0049 0.0064 0.0096 0.0095 #2 A3400mm/min 0.0095 #2 A3400mm/min 0.0015 0.0025 0.0075 0.0049 0.0049 0.0049 0.0075 0.0077 0.0077	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.60 34.60 34.60 34.60 34.60 34.60 34.00 33.94 4.53 10.31 3.94 20.20 25.15 30.92 29.66 30.51	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340m/0.0016 0.0016 0.0038 0.0049 0.0069 0.0095 0.0098 0.0093 8 0.0093 #3 A340mm/min 0.0026 0.003 0.0043 0.0043 0.0043 0.0043 0.0071 0.0070 0.0070 1.0070 0.0070	29.27 umol/mir/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 33.26 13.50 135.01 33.50 135.01 33.50 135.01 33.20 25.01 24.53 10.72 14.02 14.02 14.02 14.02 14.02 14.03 15.03 14.0	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) 0.4iso(uM) 0.25 0.5 1 2.5 5 10 0.25 5 0.5 1 1 2.5 5 0.5 1 1 2.5 5 0.5 1 1 2.5 5 0.5 1 1 5 5 0 1 5 1 2 5 5 0 1 5 1 1 2 5 5 1 1 1 2 5 5 1 1 1 2 5 5 1 1 1 2 5 5 1 1 1 1	0.0072 #11 A340mm/0.0015 0.0033 0.0047 0.0065 0.0079 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0092 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0012 0.0021 #1 A340mm/min 0.0021 0.0021 #1 A340mm/min 0.0021 0.0021 #1 A340mm/min 0.0021 0.0021 0.0022 #1 A340mm/min 0.0021 0.0021 0.0022 #1 A340mm/min 0.0021 0.0021 0.0021 0.0022 0.0021 0.0022 0.0023 0.0022 0.0023 0.002	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37 33.94 umol/min/mg 4.95 10.31 13.19 16.90 25.15 30.09 30.09 30.09 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A340mm/min 0.0049 0.0084 0.0084 0.0097 0.0096 #2 A340mm/min 0.0011 0.0025 0.0095 #2 A340mm/min 0.0011 0.0025 0.0095 0.0095 0.0095 #2 A340mm/min 0.0011 0.0075 0.005	30.09 umol/min/mg 5.36 12.50 12.50 12.51 34.66 34.60 33.94 umol/min/mg 4.53 10.31 13.60 20.20 25.15 30.92 25.15 30.92 29.68 28.66 30.51	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340nm/min 0.0049 0.0085 0.0093 0.0093 0.0093 8 0.0093 #3 A340nm/min 0.0011 0.0011 0.0025 0.0093 #3 0.0043 0.0043 0.0043 0.0071 0.0070 0.0071	29.27 umol/mir/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.01 33.23 umol/mir/mg 4.55 10.72 14.02 17.73 25.97 29.27 28.86 28.86 30.09 28.86 30.09 28.86 28.86 30.09 28.97 28.86 29.86 29.86 29.86 20.86	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 d-iso(uM) 15 2.5 50 d-iso(uM) 15 2.5 50 0.5 10 15 50 0.5 50 70 0.5 50 70 0.5 50 70 0.5 50 0.5 0.5	0.0072 #1 A340mm/min 0.0015 0.0037 0.0047 0.0065 0.0079 0.0098 0.0099 0.0099 0.0095 #1 A340mm/min 0.0012 0.0025 0.0025 0.0025 0.0025 0.0073 0.0073 0.0073 0.0075 0.0075 0.0075	29.68 umol/min/mg 5.36 11.79 23.22 28.22 35.01 35.37 35.37 35.37 35.37 35.37 10.31 10.31 10.31 11.19 16.90 25.15 30.09 30.09 20.09 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A3400ms/ 0.0015 0.0035 0.0049 0.0064 0.0097 0.0097 0.0097 0.0095 #2 A3400ms/min 0.0025 0.0075 0.0	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.30 33.94 6.63 44.30 33.94 6.63 44.30 33.94 5.53 10.31 13.60 20.20 20.20 20.55 20.92 20.88 30.51 umol/min/mg	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0089 0.0098 0.0098 0.0098 0.0098 0.0093 #3 A340nm/min 0.0026 0.0034 0.0043 0.0043 0.0071 0.0070 0.0070 1.0070 0.0070 1.0070 1.0070 0.0070	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.02 7.72 28.86 30.09 umol/min/mg 29.27 29.27 29.27 29.27 29.27 29.27 29.26 30.09 umol/min/mg 29.27 29.27 29.27 29.27 29.27 29.27 29.26 30.09 umol/min/mg 29.27 29.27 29.27 29.27 29.27 29.26 30.09 umol/min/mg 29.27 29.27 29.27 29.27 29.27 29.27 29.27 29.27 29.27 29.27 29.26 20.26 20.09 20.	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 1 0 5 5 0 0 0.5 5 1 0 0.5 5 1 0 5 5 0 0 5 1 0 5 5 0 0 5 5 0 0 5 1 1 5 5 0 0 5 1 1 5 5 0 0 5 1 1 5 5 0 0 5 5 1 1 5 5 1 0 5 5 1 1 1 5 5 1 1 5 5 1 1 5 5 1 1 5 5 1 1 1 5 5 1 1 1 1 1 1 1 1 1 1 1 1 1	0.0072 #1 A340mm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0095 #1 A340mm/min 0.0012 0.0032 0.0095 #1 A340mm/min 0.0075 0.0073 0.0075	29.68 umol/min/mg 5.36 11.79 23.22 28.22 35.01 35.37 33.94 umol/min/mg 4.95 10.31 13.19 13.19 13.19 13.19 13.19 13.19 13.19 13.25,15 30.09 30.09 30.09 30.09 20.09	Vmax 36.83 km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug Vmax 38.2	0.0073 #2 A340mm/min 0.0049 0.0049 0.0084 0.0084 0.0097 0.0096 #2 A340mm/min 0.0011 0.0025 0.0095 #2 A340mm/min 0.0011 0.0025 0.0075 0.0077 0.0075 0.0077 0.0075 0.0077 0.0075 0.0077 0.0075 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0	30.09 umol/min/mg 5.250 17.51 34.66 34.60 33.94 umol/min/mg 4.53 10.31 13.60 20.20 25.15 23.0,51 13.60 25.15 29.68 28.86 30.51 umol/min/mg	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340nm/mini 0.0049 0.0085 0.0095 0.0093 0.0093 #3 A340nm/min 0.0011 0.0026 0.0093 #3 0.0043 0.0043 0.0043 0.0071 0.0070 1.0070 0.0071	29.27 unol/mir/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.05 30.02 30.05	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 10 15 25 50 0.5 50 0.5 0.5	0.0072 #1 A340mm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0073 0.0073 0.0073 0.0073	29.68 umol/min/mg 5.36 11.79 23.22 28.22 35.01 35.37 35.37 35.37 35.37 35.37 10.31 10.31 11.319 16.90 25.15 30.09 30.09 20.09 30.09 30.09 30.09 30.09	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug	0.0073 #2 A340m/min 0.0015 0.0035 0.0049 0.0064 0.0097 0.0096 0.0095 #2 0.0095 #2 0.0095 #2 0.0095 #2 0.0095 #2 0.0095 #2 0.0095 #2 0.0021 0.0095 #2 0.0021 0.0025 0.0033 0.0041 0.0027 0.0072 0.0072 0.0072 0.0072 0.0072 0.0072 0.0072 0.0072 0.0072 0.0072	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.60 34.30 33.94 umol/min/mg 5.57 520 522 16.08	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0069 0.0085 0.0093 #3 A340nm/min 0.0011 0.0026 0.0093 #3 A340nm/min A340nm/min A340nm/min 0.0073 #3 A340nm/min 0.0075 #3 A340nm/min	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 35.02 17.72 29.27 20.27	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug Vmax 37.79
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.5 1 2.5 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0 0.5 5 0 0 0.5 5 0 0 0 0 0 0 0 0 0 0 0 0 0	0.0072 #1 A340mm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0095 #1 A340mm/min 0.0012 0.0095 #1 0.0012 0.0095 #1 0.0012 0.0032 0.0032 0.0032 0.0073 0.0073 0.0075 0.0075 0.0075	29.68 unol/min/mg 5.36 11.79 16.79 23.22 28.22 35.01 35.37	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug Vmax 38.2 Km	0.0073 #2 A340m/min 0.015 0.0035 0.0049 0.0084 0.0097 0.0096 0.0095 #2 A340m/min 0.0015 0.0095 #2 A340m/min 0.0015 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 32.67 34.66 34.66 34.66 34.60 33.94 4.53 10.31 3.94 4.53 3.94 4.53 3.94 10.31 10.80 10.92 20.20 22.20 22.86 8.86 30.92 29.68 28.86 30.92 29.68 28.86 30.92 29.68 29.57 9.22 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.23 20.57 9.25 9.25 9.25 9.25 9.25 9.25 9.25 9.25	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km	0.0071 #3 A340mm/min 0.0016 0.0038 0.0049 0.0065 0.0098 0.0098 0.0098 0.0098 83 A3400mm/min 0.0011 0.0013 0.0071 0.0073 0.0073 #3 A3400mm/min A3400mm/min 0.0017 0.0073 #3 A3400mm/min 0.0017 0.0073 #3 A3400mm/min 0.0017 0.0073 0.0073 #3 A3400mm/min 0.0017 0.0073 #3 A3400mm/min 0.001 #3 A3400m	29.27 unol/mir/mg 5.72 13.58 17.51 24.65 30.37 34.66 35.01 33.23 unol/mir/mg 4.53 10.72 14.02 1	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug Vmax 37.79 Km
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.25 0.25 1 2.5 5 10 0.25 5 0.25 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.	0.0072 #1 A340mm/min 0.0015 0.0033 0.0047 0.0065 0.0079 0.0099 0.0099 0.0099 0.0099 #1 4340nm/min 0.0012 0.0025 #1 0.0025 #1 0.0027 0.0073 0.0	29.68 umol/min/mg 5.36 11.79 16.79 23.22 23.22 23.22 23.22 23.22 23.33 4.95 10.31 35.37 33.94 4.95 10.31 16.90 25.15 30.09 30.29 30.09 25.26 12.06 17.31 24.22 24.20 12.06	Vmax Mmax 1.243 Vmax 32.39 Vmax 39.09 Vmax 39.09 Vmax Xma. Xma. Xma. Xma. Xma.	0.0073 #2 A340mm/min 0.0115 0.0035 0.0049 0.0064 0.00047 0.0006 0.0095 #2 A340mm/min 0.0017 0.0007 0.0006 0.0005 #2 A340mm/min 0.0018 0.0077 1 0.0077 0.0007 #2 A340mm/min 0.0118 0.0018 0.0078 #2	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 72.51 22.87 30.66 34.60 34.30 33.94 4.53 30.92 24.60 20.20 25.15 20.66 20.60 20.20 25.65 20.65 30.51	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km 1.38	0.0071 #3 A340m/min 0.0116 0.0038 0.0049 0.00857 0.00857 0.00085 0.00857 0.00085 0.0098 0.0093 0.0093 8 0.0093 8 0.0093 8 0.0093 0.0093 8 0.0001 0.0026 0.0026 0.0071 0.0026 0.0071 0.0073 8 3 A340m/min 0.0071 0.0073 8 3 A340m/min 0.0071 0.0073 8 3 A340m/min 0.0071 0.0075 0.0071 0.0075 0.0055 0.0071 0.0075 0.0095 0.0071 0.0075 0.0055 0.0071 0.0075 0.0055 0.00	29.27 umol/min/mg 5.72 13.58 17.51 24.65 35.01 35.01 35.01 33.23 14.02 17.73 25.97 29.26 22.86 28.66 28.66 30.09 umol/min/mg 5.26 10.62 23.66 24.65 24.65 25.97 27.97	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 (d-iso(uh) 0.25 0.25 0.25 0.25 1 2.5 5 0.5 0.25 0.5 0.5 1 1 2.5 0.5 0.5 0.5 0.5 1 0.25 0.5 0.5 1 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	0.0072 #1 A340mm/min 0.015 0.0033 0.0047 0.0065 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0073 0.0073 0.0075 0.0073 0.0075 0.0073 0.0075 0.0075	29.68 umol/min/mg 5.36 11.79 11.79 12.22 28.22 28.22 28.50 35.37	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug Vmax 38.2 Km 1.23	0.0073 #2 A340m/min 0.015 0.0035 0.0049 0.0084 0.0097 0.0096 0.0097 0.0096 0.0095 0.0025 0.0075 0.0075	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 34.66 34.66 34.66 34.60 33.94 10.31 10.31 10.31 10.31 10.30 10.20 25.15 25.57 9.28 8.86 30.51 5.57 9.28 16.08 15.26 16.08 15.27 9.26 16.08 15.27 9.26 16.08 15.27 9.26 16.08 15.27 9.26 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.08 15.27 16.09 16.09 16.09 16.09 16.09 16.09 17.27 17.51 17	Vmax 36.28 Km 1.12 Protein 1.260 Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km Km 8.49	0.0071 #3 A340nm/min 0.0016 0.0038 0.0049 0.0085 0.0098 0.0098 0.0098 0.0098 0.0098 A340nm/min 0.0011 0.0021 0.0024 0.0043 0.0024 0.0043 0.0024 0.0043 0.0071 0.0070 0.000 0.000 0.000 0.000 0	29.27 umol/min/mg 5/2 13.56 13.56 12.46 36.01 35.01 35.01 35.01 35.01 35.01 35.01 35.01 37.2 4.66 35.01 35.01 37.2 4.66 30.47 25.01 29.27 28.86 30.00 29.27 28.86 30.00 29.27 28.86 30.00 29.27 29.27 28.86 30.00 29.27 29.26 16.30 3.50	Vmax 3624 Km 1.01 protein 45ug Vmax 31.13 km 1.26 Vmax 37.79 Km 1.26
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) 0.25 0.25 0.25 1 2.5 5 10 15 25 5 0.25 0.5 0.25 0.25 0.25 0.25 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.	0.072 #1 A340mm/min 0.015 0.0033 0.047 0.0065 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0017 0.0025 0.0073 #1 A340mm/min 0.0177 0.0025 0.0073 #1 A340mm/min 0.0177 0.0039 0.0056 0.0077 #1	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 28.22 28.22 28.23 28.23 23.31 35.37	Vmax Massing Vmax Vmax 32.39 protein 39ug Vmax 38.2 Km 1.23 protein 252u0	0.0073 #2 A340m/min 0.0115 0.0035 0.0049 0.0084 0.0084 0.0084 0.0095 0.0095 72 A3440m/min 0.0017 0.0075 0.0075 0.0075 0.0075 0.0077 0.0077 0.0077 0.0077 0.0077 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0015 0.0035 0.0049 0.0035 0.0057 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0035 0.0035 0.0035 0.0055 0.0075 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.06 33.94 65 34.66 34.60 33.94 33.94 33.94 33.94 33.94 33.94 25.15 30.92 29.68 28.66 28.66 55.86	Vmax 36.28 Km 1.12 protein 45ug Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km 1.38 Km 1.38	0.0071 #3 A340m/min 0.0116 0.0038 0.0049 0.0085 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0095 0.0005 8 0.0001 0.0005 8 0.0071 0.0071 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0077 0.0075 8 3 A340m/min 0.0016 0.0053 0.0053 0.0055 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570 0.00570000000000	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 45.30 33.61 35.01 33.23 10.72 14.02 14.73 25.97 29.27 28.86 28.86 28.86 30.09 umol/min/mg 5.26 30.09 umol/min/mg 5.26 30.09	Vmax 36.24 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug Vmax 37.79 Km X7.79 Km X7.79
D2HGDH W MSCV(1.0) D2HGDH W	50 (d-iso(uh) 0.25 0.25 0.25 0.25 0.25 10 15 25 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.	0.0772 #1 A340mm/min 0.0015 0.0035 0.0095 0.0098 0.0098 0.0099 0.0098 0.0099 0.0095 #1 A340mm/min 0.0055 #1 A340mm/min 0.0073 0.0073 0.0073 0.0073 0.0073 0.0073 0.0073 0.0073	29.68 umol/min/mg 5.36 11.79 11.79 12.82 22.82 22.85.01 35.37 35.37 35.37 35.37 35.37 15.19 16.19 16.19 16.19 16.19 16.19 16.19 16.19 16.19 25.15 30.09 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.00 30.	Vmax 36.83 Km 1.243 protein 32.39 Vmax 32.39 protein 39ug Vmax 38.2 Km 1.23 protein 1.23	0.0073 #2 A340mm/min 0.015 0.0035 0.0044 0.0097 0.0097 0.0097 0.0096 0.0095 #2 A340mm/min 0.0044 0.0044 0.0061 0.0075 0.0072 0.007 0.0072 0.0072 0.007 0.0072 0.0072 0.007 0.0	30.09 umol/min/mg 5.36 12.50 17.57 24.67 34.66 34.66 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 34.60 35.57 9.20 26.61 30.51 umol/min/mg 5.57 9.28 16.03 5.51 9.28 16.03 17.03 16.	Vmax Sac28 Km 1.12 Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km 1.38 Sug Sac28 Km 1.38 Sac28 Km 2.260 Sac28 Km 1.12	0.0071 #3 A340m/min 0.0116 0.0038 0.0049 0.0069 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0093 #3 #3 A340mm/min 0.0024 0.0041 0.0024 0.0041 0.0024 0.0041 0.0024 0.0070 0.0004 0.0007 0.0004 0.0007 0.0007 0.0070 0.0050 0.0050 0.0050 0.0050 0.00510000000000	29.27 umol/min/mg 5.72 13.56 13.56 13.56 13.50 30.37 4.66 35.01 35.01 35.01 35.01 35.01 14.02 17.73 26.97 29.27 28.86 30.09 umol/min/mg 5.26 10.82 16.30 33.48 30.33 46 30.33 46 30.33 40.03 33.48 35.01 33.48 45.03 45.03 4	Vmax 3624 Km 1.01 protein 45ug Vmax 31.13 km 1.26 protein 39ug Vmax 39ug
D2HGDH W MSCV(1.0) D2HGDH W	50 T(0.75ug) d-iso(uM) 0.25 0.25 0.5 1 2.5 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.25 5 0 0.5 5 1 1 2.5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 5 0 0 5 5 0 0.5 5 0 0.5 5 0 0.5 5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 0 0.5 5 5 5 5 0 0.5 5 5 5 5 5 5 5 5 5 5 5 5 5	0.072 #1 A340mm/min 0.015 0.0033 0.0047 0.0065 0.0099 0.0099 0.0099 0.0099 0.0099 0.0099 0.0095 #1 A340mm/min 0.0017 0.0025 0.0073 #1 A340mm/min 0.0017 0.001 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	29.68 umol/min/mg 5.36 11.79 16.79 23.22 28.22 28.22 28.22 28.23 23.31 35.37 33.94 4.95 10.31 16.90 25.15 30.09 25.15 30.09 25.26 12.06 17.31 24.42 33.30 12.26 17.31 24.42 36.17 36.17	Vmax 36.83 Km 1.243 protein 45ug Vmax 32.39 Km 1.49 protein 39ug Vmax 38.2 Km 1.23 protein 25ug	0.0073 #2 A340mm/min 0.0115 0.0035 0.0049 0.0064 0.0084 0.0084 0.0095 0.0095 #2 A340mm/min 0.0011 0.0025 0.0075 0.0075 0.0075 0.0077 0.0075 0.0077 1 0.0025 0.0077 0.0077 1 0.0025 0.0077 1 0.0018 0.0	30.09 umol/min/mg 5.36 12.50 17.51 22.87 30.01 33.94 4.53 30.01 33.94 umol/min/mg 4.53 30.92 25.15 30.92 22.9.68 28.86 28.86 28.29 30.51 umol/min/mg 5.57 9.28 16.08 24.73 30.66 53.58 66 53.58 66 55.57 35.56	Vmax 36.28 Km 1.12 Vmax 31.82 Km 1.260 protein 39ug Vmax 38.49 Km 1.38 protein 52ug	0.0071 #3 A340mm/min 0.0116 0.0038 0.0049 0.0085 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 0.0098 4.0098 0.0098 73 A340mm/min 0.0017 0.0026 0.0071 0.0073 83 A340mm/min 0.0177 0.0035 0.0063 0.0071 0.0073 #3 A340mm/min 0.017 0.0035 0.0063 0.0071 0.0073 0.0063 0.0063 0.0063 0.0064 0.0041 0.0017 0.0035 0.0063 0.0063 0.0064 0.0041 0.0015 0.0063 0.0064 0.0041 0.0015 0.0063 0.0063 0.0064 0.0041 0.0015 0.0064 0.0041 0.0015 0.0063 0.0063 0.0063 0.0063 0.0063 0.0064 0.0041 0.0015 0.0063 0.0064 0.0064 0.004 0.	29.27 umol/min/mg 5.72 13.58 17.51 24.65 30.37 4.53 10.73 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.02 14.63 30.09 umol/min/mg 5.26 30.09	Vmax 36.24 Km 1.01 protein 45ug Vmax 37.79 Km Xmax 37.79 Km Xmax 37.79 Km Xmax 37.79

Enzyme kinectis calculated using the Michaelis-Menten equation

Supplementary Table 5 (continued) Transient knockdowr OCI-Ly8 KD #3 A340nm/min 0.0009 #1 #2 siRNA ctrl A340nm/min 0.0009 A340nm/mi 0.0008 Vmax 49.91 umol/min/mg Vmax 48.00 nol/min/mg nol/min/mg Vmax 48.21 d-iso(uM) 3.36 2.99 3.36 0.25 0.0017 6.36 0.0015 5.61 0.0016 5.98 0.5 0.0031 11.59 Km 0.0030 11.22 Km 0.0035 13.09 Km 0.0065 24.30 2.24 0.0068 25.42 2.31 0.0069 25.80 2.13 39.26 41.13 42.25 0.0108 0.0117 0.0115 40.38 43.74 43.00 44.49 44.12 0.0102 0.0115 0.0114 38.14 43.00 42.62 2.5 0.0105 5 10 15 25 0.0113 42.62 0.0114 0.0119 0.0116 43.37 0.0115 43.00 0.0118 0.0114 42.62 50 D2HGDH siRNA #3 d-iso(uM) #1 #2 #3 nol/min/mg #2 A340nm/mi 0.0008 0.0012 nol/min/mg A340nm/mi Vmax 40.78 A340nm/mi Vmax 39.5 Vma nol/min/n 2.44 6.33 14.13 3.90 5.85 13.64 3.41 7.79 12.67 0.0005 40.61 0.0007 0.25 0.5 Km 2.25 Km 2.2 Km 1.84 0.0026 0.0029 0.0028 19.97 0.0041 0.0040 19.49 0.0045 21.92 2.5 0.0058 28.26 0.0060 29.23 0.0065 31.67 0.0070 34.10 0.0075 36.54 36.54 0.0072 35.08 5 10 15 25 50 36.05 38.49 36.54 35.08 35.56 36.54 35.56 0.0074 0.0075 0.0073 0.0074 0.0075 37.03 36.54 0.0075 #1 #3 #2 D2HGDH siRNA #5 A340nm/min A340nm/min umol/min/mg Vmax A340nm/mir umol/min/mg Vmax umol/min/mg Vmax 41.57 d-iso(uM) 0.0003 1.79 41.6 0.0003 1.79 42.65 0.0007 4.17 7.74 6.55 13.10 23.22 29.77 0.25 0.0011 0.0010 5.95 0.0013 5.95 14.29 19.05 30.37 0.0022 0.0013
0.0023
0.0030
0.0052 13.70 17.86 30.96 0.5 Km 2.1 0.0024 Km 2.35 Km 0.0024 0.0032 0.0051 2.17 2.5 0.0060 35.73 0.0065 38.70 0.0064 38.11 5 10 15 25 50 0.0065 38.70 0.0063 37.51 0.0064 38.11 0.0063 37.51 0.0064 38.11 0.0062 36.92 0.0063 37.51 0.0064 38.11 0.0062 36.92 Ramos KD #1 #3 siRNA ctrl A340nm/min umol/min/mg Vmax A340nm/mi umol/min/mg Vmax A340nm/min umol/min/mg Vmax 25.49 25.4 d-iso(uM) 0.0012 3.86 0.0013 4.18 25.92 0.0013 4.18 0.25 0.0026 8.36 0.0027 8.68 0.0026 8.36 12.54 18.01 21.54 22.51 Km 1.04 12.22 18.33 21.86 22.83 Km 1.06 12.22 18.01 20.90 22.51 Km 1.07 0.5 0.0039 0.0038 0.0038 0.0039 0.0056 0.0067 0.0070 0.0076 0.0038 0.0056 0.0065 0.0070 0.0078 0.005 0.0057 0.0068 0.0071 0.0078 2.5 5 10 15 25 50 24.44 25.08 25.08 0.0076 24.44 0.0077 24.76 0.0075 24.12 0.0075 24.12 0.0077 24.76 0.0076 24.44 #1 2 #3 D2HGDH siRNA #3 d-iso(uM) #1 A340nm/n 0.0012 0.0021 2 340nm/m 0.0012 0.0022 #3 A340nm/mii 0.0012 0.0021 4.02 7.03 21.76 4.02 7.37 21.88 4.02 7.03 21.45 0.25 Km 1.07 0.5 0.0030 10.05 0.0032 10.72 Km 0.97 0.0031 10.38 Km 1.12 0.0043 14.40 0.0049 16.41 0.0041 13.73 19.76 20.10 20.10 21.10 20.10 18.42 20.10 21.10 20.77 2.5 5 10 15 25 50 0.0059 0.0055 0.0051 17.08 0.0059 0.0060 0.0060 0.0063 0.0060 0.0055 0.0060 0.0063 0.0062 0.0062 0.0051 0.0061 0.0062 0.0060 0.0061 17.08 20.43 20.77 20.10 20.77 20.43 #1 #3 2 D2HGDH siRNA #5 A340nm/min mol/min/mo Vmax A340nm/mir nol/min/mo Vmax A340nm/min mol/min/mo Vmax 19.68 0.0012 0.0024 0.0032 0.0044 0.0051 3.94 7.87 10.50 14.44 16.73 0.0011 0.0024 0.0033 0.0039 3.61 7.87 10.83 12.80 16.08 0.0011 0.0025 0.0033 0.0039 3.61 7.87 10.83 12.80 d-iso(uM) 19.25 19.68 0.25 0.5 Km 0.81 Km 0.93 Km 0.93 2.5 0.0049 0.0049 16.08 0.0055 18.05 0.0055 18.05 0.0056 18.05 5 10 15 25 50 0.0055 18.05 0.006 19.69 0.0059 19.69 18.70 19.36 18.70 19.36 0.0054 17.72 0.0057 0.0062 0.0060 19.69 0.0059 0.0060 Stable knockdown HEK-293 #1 2 #3 siRNA ctrl A340nm/min nol/min/ma A340nm/mir nol/min/mo Vmax A340nm/min mol/min/mo Vmax 30.09 Vmax 0.0027 0.0037 0.0061 8.68 11.90 19.61 9.00 12.54 21.86 22.51 0.0025 0.0048 0.0070 d-iso(uM) 30.58 0.0028 30.85 8.04 0.0039 15.43 22.51 0.25 Km 0.66 Km 0.56 Km 0.49 0.0070 0.0071 22.83 0.0069 22.19 2 0.0083 26.69 0.0088 28.30 0.0084 27.01 4 0.0085 27.33 0.0093 29.90 0.0085 27.33 5 10 15 25 50 0.0093 29.90 0.0094 30.23 0.0089 28.62 0.0089 0.0091 0.0090 0.0093 0.0090 28.94 0.0092 29.58 29.26 28.94 0.0091 28.62 28.94 29.26 0.0089 29.58 0.0090 29.90 #1 2 #3 D2HGDH siRNA #3 A340nm/min umol/min/ma A340nm/mir umol/min/ma Vmax A340nm/min umol/min/ma Vmax Vmax 25.43 d-iso 0.0020 6.43 25.26 0.0022 7.07 24.63 0.0020 6.43 14.15 0.25 0.0032 10 29 0.0035 11 25 0 0044 0.0032 0.0050 0.0059 0.0066 0.0068 10.29 16.08 18.97 21.22 21.86 11.25 17.04 18.01 20.26 Km 0.59 0.0044 0.0053 0.0059 0.0072 14.15 17.04 18.97 23.15 23.47 0.5 0.0000 km km 0.0053 0.0056 0.0063 0.0065 0.67 0.51 20.90 23.79 0.0073 0.0076 24.44 0.0074 0.0078 25.08 23.47 0.0075 24.12 0.0075 24.12 0.0073

5 10 15 25 50 0.0076 24.44 0.0075 24.12 0.0078 25.08 0.0077 24.76 0.0078 25.08 0.0077 24.76 #1 A340nm/min #3 A340nm/min D2HGDH siRNA #5 A340nm/mir umol/min/mg Vmax umol/min/mg umol/min/mg Vmax d-iso 0.0023 7.40 11.58 26 0.0022 7.07 25.91 0.0024 7.72 0.25 0.0036 0.0036 11.58 0.0041 13.18 11.58 19.61 18.33 22.19 23.47 25.08 25.08 13.18 18.65 19.94 24.12 22.51 25.08 24.44 17.68 21.54 23.79 24.12 24.44 0.5 0.0055 Km 0.0061 Km 0.0058 0.0055 0.0067 0.0074 0.0075 0.0076 0.0058 0.0062 0.0075 0.0070 0.0078 0.53 0.0057 0.56 0.0057 0.0069 0.0073 0.0078 10 15 0.0077 24.76 0.0078 0.0076 0.0078 25.08 0.0079 25.40 0.0079 25.40 25 0.0078 25.08 0.0079 25.40 0.0080 25.72

Vmax 25.85

Km

0.49

Enzyme kinectis calculated using the Michaelis-Menten equation

50

Supplementary Table 6. IDH activiity assay in subcellular fractions

Cytosolic fraction										
MSCV	A	340nm/mir	า	um	ol NADPH/min	/mg	mean	SD		
D-isocitrate(uM)	#1 ;	¥2 7	#3	#1	#2	#3	umolNADPH/min/ma			
0.25	0.0014	0.0013	0.0013	4.33	4.02	4.02	4.12	0.18		
0.5	0.0020	0.0021	0.0019	6.18	6 4 9	5.87	6.18	0.31	Best fit values	Std Error
1	0.0035	0.0034	0.0033	10.82	10.51	10.20	10 51	0.31	Vmax	0101 21101
25	0.0040	0.0039	0.0039	12 37	12.06	12.06	12.16	0.18	17.65	0.26
5	0.0049	0.0000	0.0050	15 15	14.84	15.46	15 15	0.10	17.00 Km	0.20
10	0.0043	0.0040	0.0055	16 70	17.62	17.00	17 11	0.01	0	0.0585
25	0.0053	0.0054	0.0058	16.30	16.70	17.00	17.00	0.97	0	0.0000
25	0.0053	0.0054	0.0057	16.33	17.06	17.55	17.00	0.02		
50	0.0000	0.0000	0.0007	10.44	17.00	17.00	11.00	0.02		
D2HGDH WT	A	340nm/mir	n	um	ol NADPH/min	/mg	mean	SD		
D-isocitrate(uM)	#1 ;	#2 #	#3	#1	#2	#3	umoINADPH/min/mg			
0.25	0.0013	0.0014	0.0013	3.88	4.18	3.88	3.98	0.17		
0.5	0.0019	0.0020	0.0020	5.68	5.98	5.98	5.88	0.17	Best fit values	Std. Error
1	0.0034	0.0035	0.0032	10.16	10.46	9.56	10.06	0.46	Vmax	
2.5	0.0039	0.0040	0.0040	11.65	11.95	11.95	11.85	0.17	17.77	0.27
5	0.0050	0.0050	0.0052	14.94	14.94	15.54	15.14	0.35	Km	
10	0.0058	0.0057	0.0059	17.33	17.03	17.63	17.33	0.30	0.9171	0.0641
25	0.0057	0.0058	0.0056	17.03	17.33	16.73	17.03	0.30		
50	0.0057	0.0058	0.0055	17.09	17.39	16.49	16.99	0.46		
Mitochondrial fraction										
MSCV	A	340nm/mir	ı	um	ol NADPH/min	/ma	mean	SD		
D-isocitrate(uM)	#1 ;	¥2 i	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0 0004	0 0003	0.0004	11 69	8 77	11 69	10.72	1 69		
0.5	0.0006	0.0007	0.0006	17.54	20.46	17.54	18.51	1 69	Best fit values	Std Error
1	0.0011	0.0010	0.0012	32 15	29.23	35.08	32 15	2 92	Vmax	0101 21101
25	0.0013	0.0010	0.0012	38.00	40.92	38.00	38 97	1 69	58.8	1 18
5	0.0017	0.0014	0.0016	49.69	46.77	46 77	47 74	1.60	60.0 Km	1.10
10	0.0017	0.0010	0.0010	55 54	58.46	58.46	57 49	1.69	1 018	0.0932
25	0.0019	0.0020	0.0020	55 54	55 54	58.46	56 51	1.69	1.010	0.0352
50	0.0021	0.0018	0.0018	61.58	52.79	52.79	55.72	5.08		
DALLODU WT						/		CD		
	A.	5400000/0000	1 #0	um #4		/mg		5D		
D-Isocitrate(UNI)	#1 1	¥Z ¥	#3	#1	#2	#3		4.00		
0.25	0.0005	0.0006	0.0005	14.62	17.54	14.62	15.59	1.69	Deetfituelus	
0.5	0.0008	0.0009	0.0008	23.38	20.31	23.38	24.30	1.69	Best nt values	Sta. Error
1	0.0016	0.0015	0.0015	46.77	43.85	43.85	44.82	1.69	Vmax	4.00
2.5	0.0019	0.0017	0.0019	55.54	49.69	55.54	53.59	3.38	84.3	1.66
5	0.0025	0.0024	0.0025	73.08	70.15	73.08	/2.10	1.69	Km	0.00.1-
10	0.0028	0.0029	0.0028	81.85	84.77	81.85	82.82	1.69	1.063	0.0948
25	0.0027	0.0028	0.0027	78.92	81.85	78.92	79.90	1.69		
50	0.0027	0.0027	0.0026	79.18	79.18	76.25	78.20	1.69		

Enzyme kinectis calculated using the Michaelis-Menten equation

Supplementary Table 6 (continuation)

Cytosolic fraction										
siRNA ctrl	A	A340nm/mi	in	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0018	0.0017	0.0016	5.10	4.82	4.54	4.82	0.28		
0.5	0.0025	0.0024	0.0025	7.09	6.81	7.09	6.99	0.16	Best fit va	Std. Error
1	0.0042	0.0041	0.0041	11.91	11.63	11.63	11.72	0.16	Vm	ax
2.5	0.0048	0.0047	0.0046	13.61	13.33	13.04	13.33	0.28	17.99	0.24
5	0.0058	0.0057	0.0056	16.45	16.16	15.88	16.16	0.28		
10	0.0063	0.0062	0.0061	17.86	17.58	17.30	17.58	0.28	Ki	m
25	0.0061	0.0062	0.0060	17.30	17.58	17.01	17.30	0.28	0.6772	0.044
50	0.0059	0.0064	0.0060	16.78	18.21	17.07	17.35	0.75		

D2HGDH siRNA #3	A	\340nm/mi	n	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0015	0.0016	0.0014	4.54	4.84	4.24	4.54	0.30	Best fit va	Std. Error
0.5	0.0021	0.0021	0.0023	6.36	6.36	6.96	6.56	0.35	Vm	ax
1	0.0037	0.0038	0.0036	11.20	11.51	10.90	11.20	0.30	17.66	0.24
2.5	0.0043	0.0044	0.0042	13.02	12.72	12.72	12.82	0.17	Ki	n
5	0.0052	0.0053	0.0051	15.74	16.05	15.44	15.74	0.30	0.7263	0.048
10	0.0056	0.0057	0.0055	16.96	17.26	16.65	16.96	0.30		
25	0.0057	0.0059	0.0055	17.26	17.86	16.65	17.26	0.61		
50	0.0055	0.0058	0.0054	16.71	17.62	16.40	16.91	0.63		

D2HGDH siRNA #5	A	A340nm/mi	n	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0013	0.0012	0.0012	4.25	3.92	3.92	4.03	0.19	Best fit va	Std. Error
0.5	0.0018	0.0019	0.0018	5.88	6.21	5.88	5.99	0.19	Vm	ax
1	0.0032	0.0033	0.0031	10.46	10.78	10.13	10.46	0.33	17.57	0.21
2.5	0.0039	0.0041	0.0038	12.74	13.40	12.42	12.85	0.50	Kı	m
5	0.0048	0.0047	0.0048	15.69	15.36	15.69	15.58	0.19	0.8098	0.046
10	0.0052	0.0051	0.0052	16.99	16.67	16.99	16.88	0.19		
25	0.0052	0.0051	0.005	16.99	16.34	16.34	16.56	0.38		
50	0.0051	0.0052	0.0052	16.72	17.05	17.05	16.94	0.19		

Mitochondrial fraction										
siRNA ctrl	A	\340nm/mi	n	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0007	0.0006	0.0007	17.29	14.82	17.29	16.46	1.43		
0.5	0.0009	0.0010	0.0010	22.23	24.70	24.70	23.87	1.43	Best fit va	Std. Error
1	0.0019	0.0019	0.0017	46.92	46.92	41.98	45.28	2.85	Vn	nax
2.5	0.0024	0.0025	0.0023	59.27	61.74	56.80	59.27	2.47	84.92	1.42
5	0.0030	0.0029	0.0028	74.09	71.62	69.15	71.62	2.47		
10	0.0033	0.0035	0.0032	81.50	86.44	79.03	82.32	3.77	К	m
25	0.0034	0.0032	0.0032	83.97	79.03	79.03	80.67	2.85	1.012	0.07732
50	0.0031	0.0033	0.0032	76.80	81.76	79.28	79.28	2.48		

D2HGDH siRNA #3	A	A340nm/mi	n	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0003	0.0004	0.0002	9.74	12.99	6.50	9.74	3.25	Best fit va	Std. Error
0.5	0.0005	0.0005	0.0004	16.24	16.24	12.99	15.16	1.88	Vm	ax
1	0.0009	0.0009	0.0008	29.23	29.23	25.98	28.15	1.88	55.35	1.20
2.5	0.0012	0.0011	0.0011	38.97	35.73	35.73	36.81	1.88	Ki	n
5	0.0014	0.0015	0.0014	45.47	48.72	45.47	46.55	1.88	1.105	0.108
10	0.0016	0.0018	0.0015	51.97	58.46	48.72	53.05	4.96		
25	0.0017	0.0016	0.0015	55.21	51.97	48.72	51.97	3.25		
50	0.0016	0.0017	0.0015	52.13	55.39	48.88	52.13	3.26		

D2HGDH siRNA #5	A	A340nm/mi	in	umol	NADPH/m	in/mg	mean	SD		
D-isocitrate(uM)	#1	#2	#3	#1	#2	#3	umolNADPH/min/mg			
0.25	0.0005	0.0004	0.0005	14.59	11.67	14.59	13.62	1.68	Best fit va	Std. Error
0.5	0.0007	0.0006	0.0006	20.42	17.51	17.51	18.48	1.68	Vm	nax
1	0.0011	0.0010	0.0011	32.10	29.18	32.10	31.12	1.68	54.4	0.89
2.5	0.0013	0.0012	0.0013	37.93	35.01	37.93	36.96	1.68	K	m
5	0.0016	0.0015	0.0016	46.69	43.77	46.69	45.71	1.68	0.8854	0.068
10	0.0018	0.0017	0.0018	52.52	49.60	52.52	51.55	1.68		
25	0.0019	0.0018	0.0017	55.44	49.60	49.60	51.55	3.37		
50	0.0019	0.0018	0.0019	55.62	52.69	55.62	54.64	1.69		

Enzyme kinectis calculated using the Michaelis-Menten equation

Supplementary Table 7 - Mutational status of chromatin modifiers in DLBCL cell lines

Cell line	D2HGDH	MLL2	MLL3	MLL4	MLL5	CREBBP	EP300	EZH2
WSU-NHL	Mutant	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	Mutant ¹⁻³	WT ¹⁻³	WT ¹⁻³
OCI-Ly7	Mutant	WT ¹⁻³	Mutant ²	WT ²	WT ²	WT ^{1-3,5}	WT ^{1-3,5}	WT ^{1-3,5}
SU-DHL6	Mutant	Mutant ^{1,3,5}	WT ^{1,3,5}	WT ^{1,3,5}	WT ^{1,3,5}	WT ⁵ ; Mutant ^{1,3}	Mutant ^{1,3,5,7}	Mutant ^{1,3,5,6}
SU-DHL8	Mutant	Mutant ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	Mutant ^{1,3}	Mutant ^{1,3,7}	WT ^{1,3,7}
SU-DHL4	WТ	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ^{1,3} Del ⁷	WT ^{2,7} , Mutant ^{1,3}
SU-DHL10	WТ	Mutant 1,3	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	Mutant ^{1,3}	Mutant ^{1,3,7}	WT ^{1,3,7}
OCI-Ly1	WT	Mutant ^{1,3,5}	WT ^{1-3,5,6}	WT ^{1-3,5,6}	WT ^{1-3,5,6}	Mutant ^{1,3} WT ^{2,5}	WT ¹⁻⁶	Mutant ^{1-3,5,6}
OCI-Ly4	WТ	Mutant ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}
OCI-Ly18	WT	Mutant ^{1,3}	WT ¹	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}
SU-DHL2	WТ	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	Del ^{1,3}	WT ^{1,3}
Farage	WT	WT ²	WT^2	WT ²	WT ²	WT^2	WT ²	WT^2
OCI-Ly8	WT	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	Mutant ^{1,3} WT ²	WT ^{1,3,4}	WT ¹⁻³
OCI-Ly10	WT	WT ¹⁻³	WT ¹⁻⁴	WT ¹⁻⁴	WT ¹⁻⁴	WT ¹⁻⁴	WT ^{1,3,4} M ⁷	WT ^{1-4,7}
OCI-Ly19	WT	WT ^{2,5}	WT ^{2,5}	WT ^{2,5}	WT ^{2,5}	WT ^{2,5}	WT ^{2,5}	WT ^{2,5,7}

The cell lines analyzed for the histone and DNA methylation, HIF hydroxylation and alpha-KG or D2-HG levels (Figure 7 and Supplementary Figure 12) are listed above. The remaining cell lines sequenced for D2HGDH (Supplementary Table1) are listed below.

MLL2 and MLL3 encode histone methyltransferase that methylates H3K4; MLL2 and MLL3 mutations are likely loss-of-function thus leading to lower methylation of H3K4, yet cell lines mutant for both D2HGDH and MLL2 or MLL3 display high H3K4me3 levels.

The methylation of H3K4m3 was higher in OCI-Ly7, SU-DHL6 and SU-DHL8, than in SU-DHL10, OCI-Ly1, OCI-Ly1 or OCI-Ly18 and thus appear to be driven by D2HGDH

Cell line	D2HGDH	MLL2	MLL3	MLL4	MLL5	CREBBP	EP300	EZH2
HBL-1	WT	WT ^{1,3,4}	WT ^{1,3} M ⁴	WT ^{1,3,4}	M^4	WT ^{1,3} M ⁴	WT ^{1,3,4}	WT ^{1,3,4}
HT	WT	WT ²	WT ²	WT ²	WT ²	WT ²	WT ²	WT ^{2,7}
K1106P	WT	NA	NA	NA	NA	NA	NA	NA
K422	WT	WT ^{2,6} M ⁵	WT ^{2,5,6}	WT ^{2,5,6}	WT ^{2,5,6}	$WT^2 M^5$	M ⁵	M ^{2,5,6}
OCI-Ly3	WT	WT ¹⁻⁴	WT ¹⁻⁴	M^4	WT ¹⁻⁴	WT ¹⁻⁴	WT ¹⁻⁴	WT ¹⁻⁴
NU-DHL1	WT	M ⁵	WT ⁵	WT ⁵	WT ⁵	M ⁵	WT ⁵	WT ^{5,7}
NU-DUL1	WT	M ⁵	WT ⁵	WT ⁵	WT ⁵	WT ⁵	WT ⁵	WT ^{5,7}
Pfeiffer	WT	$WT^2 M^5$	WT ²	WT ²	WT ²	M ²	M ⁷	WT ^{2,7}
RC-K8	WT	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	Del ^{1,3}	WT ¹⁻³
SU-DHL5	WT	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	WT ^{1,3}	Del ^{1,3}	WT ^{1,3} Del ⁷	Del ^{1,3,7}
SU-DHL7	WT	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ² M ^{1,3}	WT ¹⁻³	WT ¹⁻³
SU-DHL16	WT	NA	NA	NA	NA	NA	NA	NA
Toledo	WT	M ⁵	$WT^2 M^7$	WT ^{2,5}	WT ^{2,5}	WT ^{2,5}	M ⁷	WT ^{2,5,7}
U2932	WT	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³	WT ¹⁻³
USC-DHL1	WT	NA	NA	NA	NA	NA	NA	NA

Supplementary Table 8 - Mutational status of chromatin modifiers in DLBCL

Tumor ID	D2HGDH	MLL2 (% variant allele)	MLL3 (% variant allele)	MLL4	MLL5	EZH2 (% variant allele)	EP300 (% variant allele)	CREBBP (% variant allele)	TET2
		c.C11968T:p.Q3990X (25%);							
2202	WT	c.C6520T:p.Q2174X (37%)	WT	WT	WT	WT	c.C5597T:p.P1866L (34%)	WT	WT
3416	WT	WT	c.C5636T:p.P1879L (20%)	WT	WT	WT	WT	WT	WT
4236	WT	WT	WT	WT	WT	WT	WT	WT	WT
4522	WT	WT	WT	WT	WT	WT	WT	WT	WT
5234	A426T	WT	WT	WT	WT	WT	WT	WT	WT
5485	WT	c.A15176T:p.H5059L (82%)	WT	WT	WT	c.A1769T:p.Y641F (38%)	c.T4197G:p.D1399E (39%)	c.C4378T:p.R1460X (78%)	WT
6902	A426T	WT	WT	WT	WT	WT	WT	WT	WT
7518	WT	c.10982delG:p.G3661fs (67%)	WT	WT	WT	c.C1907T:p.A687V (17%)	WT	WT	WT
7572	WT	WT	WT	WT	WT	WT	c.4057delT:p.F1353fs (40%)	WT	WT

Supplementary Table 9 - D2HGDH mutational status in cancer

Tumor Type	Mutation - aa modification	Frequency*	Somatic Status	References
Glioma (GBM) Endometrioid carcinoma	M153T, S178G, S197T, N443S R107Q, V142I, A170V, R215Q, A420T	<1% 1.2%	confirmed somatic somatic or unknown	TCGA (COSU329, COSU545) and Nature Genetics 2013;45(10):1141-9 TCGA (COSU419)
Colon Rectal Cancer	G98S, S197G [#] , D403N, L505M	4.7% (3/70 cases) #cell line	confirmed somatic	Nature 2012;488:660-4
Lung adenocarcinoma/squamous cel	Q129H, S149F, G201W, K252N, T390K, G438C, A455T	<1%	somatic or unknown	TCGA (COSU417/418); Cell 2012;150(6):1107-20; Nature Genetics 2012, 44(10):1104-10 and :1111-€
Melanoma	P141L, R215*, F336L, P424L, E447K, E475K	1.7%	confirmed somatic	TCGA (COSU540)
Stomach - adenocarcinoma	G193R, A373T, D413L	<1%	confirmed somatic	TCGA (COSU413/)
Bladder	A446T, G477A,	<1%	confirmed somatic	TCGA (COSU541/581)
Burkitt Lymphoma	C172Y	<1%	unknown	Nature 2012;490:116-20

Green font - same residue was reoprted mutated in D-2-hydroxyglutaric aciduria (D2-HGA Red font - same mutation found in D2:HGA patients When it was investigated, all mutations were found to be heterozygou

*To be more stringent, all SNPs - rare or frequent - were removed from this analysis, even when the variant was described in COSMIC as a somatic ever

Supplementary Table 10 – Primers sequence

D2HGDH – PCR and sequencing

D-HGex2F 5'-TGCTTCTGCAAGCGTGTTTC-3' D-HGex2R 5'-TTTGAAGCCTCCACGGGAAG-3' D-HGex3F 5'-GAGTGACCACTTGCCTCATC-3' D-HGex3R 5'-AACCAAGATGTCATCGGCTG-3' D-HGex4F 5'-GCAGGGTAATCAGGATTTGG-3' D-HGex4R 5'-GCCCTAACTCATTCACCCAC-3' D-HGex5F 5'-GTTCCTTCTGGGTGGCTTG-3' D-HGex5R 5'-ATGAGAGCCGTGAGAGGAC-3' D-HGex6F 5'-GTCCATCCTTCAGCCTCTTG-3' D-HGex6R 5'-CTTCCTCACACCAACAGTG-3' D-HGex7F 5'-TGTTTGTTGCAGTGCCAGTC-3' D-HGex7R 5'-TGTGTCCAGACGTGCAGAAG-3' D-HGex8F 5'-TCTTGGCCACGAAAGATCAG-3' D-HGex8R 5'-CTGTCTAGGCTGCACCAATG-3' D-HGex9F 5'-ATACAGAACATGCTGCTGCC-3' D-HGex9R 5'-GATATGCTAAGCCAGAGACC-3' D-HGex10F 5'-ATCTTGGGAGGGGGCTGTTG-3' D-HGex10R 5'-TTGGCAGCAGCAGGAGTG-3'

L2HGDH – PCR and sequencing

L-HGex1F 5'-AAGGCGCGCCACTTCATTG-3' L-HGex1R 5'-CGGGACAGGGAAATACGAAC-3' L-HGex2F 5'-TGCATGTGAAGTTTGGCGAG-3' L-HGex2R 5'-CACTGACATTCAGCATGAAAG-3' L-HGex4F 5'-CTCCTTTGGGTCATACAATAG-3' L-HGex4R 5'-CTGTGACAGGATTATCTAACTG-3' L-HGex5F 5'-TAGCAGCAAGAAAAGCTTGG-3' L-HGex5R 5'-ATGGAGGGCTGACTATATTC-3' L-HGex6F 5'-GGTGCAATCATAGTAATGAC-3' L-HGex6R 5'-ACTTAAAATACAGCCCTGTG-3' L-HGex7F 5'-CCCTCTTGACCTATTCTAC-3' L-HGex7R 5'-CATCTCCTTTATGACCACC-3' L-HGex8F 5'-TGCATGAGAAGAAGTGTTTTATG-3' L-HGex8R 5'-CCAATCACAAATATGGGGGATTTAC-3' L-HGex9F 5'-GCCTAGATTTTTGTGATGAC -3' L-HGex9R 5'-GTATTTACACTCCTTATCCC -3' L-HGex10F 5'-CGCTGACTTGTAAAGTATCC-3' L-HGex10R 5'-TGCAGTGGTTATCTTTGACC-3'

IDH1/IDH2 – PCR and sequencing

IDH1F 5'-GAGCTCTATATGCCATCACTGC-3' IDH1R 5'-CAAGTTGGAAATTTCTGGGC-3' IDH2F 5'-ATTCTGGTTGAAAGATGGCG-3' IDH2R 5'-ACAAGAGGATGGCTAGGCG-3'

D2HGDH – cloning, mutagenesis, RT-PCR

D2HGDH – siRNA

D2HGDH shRNA #3 target sequence: CTGTCATGAATGTCCAGTA 5'- GATCCTGTCATGAATGTCCAGTAATTCAAGAGATTACTGGACATTCATGACAGAA - 3' 5' - AGCTTTCTGTCATGAATGTCCAGTAATCTCTTGAATTACTGGACATTCATGACAGA - 3' D2HGDH shRNA #5 target sequence: CCCAGCTGGGAAGACAGTT 5' - GATCCCCAGCTGGGAAGACAGTTATTCAAGAGATAACTGTCTTCCCAGCTGGCAA - 3' 5' - AGCTTTGCCAGCTGGGAAGACAGTTATTCTAATAAACTGTCTTCCCAGCTGGCAA - 3'

D2HGDH – tagged constructs

D2HGDH cloning into pHM6 – n-terminus HA tag: D2HAFw-HindIII – ataagcttgCTGCCCGTCGGCCTCT D2HARv-NotI - aagcggccgcgaGGCCTGGCTGGGCA

D2HGDH cloning into p3xFLAG-CMV – c-terminus FLAG tag: D2FlagFw-HindIII - ataagcttGAGCCCGAGGTCTCCGTC D2FlagRv-BamHI - ttggatccGGCCTGGCTGGCAGCGT

IDH2 - cloning and RT-PCR oligos

IDH2F-XhoI - tactcgagTCTCCAGCTTGGGATG IDH2R-EcoRI - gagaattcCTCCACTGCAGCCATG IDH2-QPCR-Fw 5' AGCTGGATGGGAACCAAGAC 3' (exon 9) IDH2-QPCR-Rv 5' CTCGTTCAGCTTCACATTGC 3' (exon 11)

Supplementary Table 11. Antibodies validation

Antibody	Commercial source	Validation
D2HGDH	Proteintech, #13895-1-AP	Antibodypedia
H3K4me3	Cell Signaling Technologies #9751	Nature 483, 474-78 (2012).
H3K9me2	Cell Signaling Technologies #9753	Nature, 464:306-10 (2010)
H3K27me3	Cell Signaling Technologies #9733	Nature, 464:306-10 (2010)
H3K36me3	Cell Signaling Technologies #4909	Nature, 469:231-05 (2011)
H3K79me2	Cell Signaling Technologies #9757	Nature 483, 474-78 (2012)
Total histone H3	Cell Signaling Technologies #4499	J Immunol 186:3986-96 (2011).
HIF1α	BD Biosciences #61095	1degreebio.org
HIF1α-hydroxyproline (Pro402)	Millipore #07-1585	J. Biol. Chem., 286: 13041-51 (2011)
GLUT1	Novus Biologicals # NB300-666	Antibodypedia
IDH1	Cell Signaling Technology #8137	Science 324:261-5 (2009)
IDH2	Abcam, #ab55271	Nature 483, 474-78 (2012)
β-actin	Sigma-Aldrich, #A2228	1degreebio.org

Supplementary Table 12 - Metabolites quantification

D2HGDH stable expression cell model

D2-HG pmol/mg of protein - a	assay#1, 5 i	replicates			
MSCV	8.431277	9.934035	15.45281	13.72072	12.26284
D2HGDH - WT	1.502575	1.806834	2.834707	2.913745	2.851159
D2HGDH - G131X	8.921748	9.508083	7.696046	6.301116	6.145552
D2HGDH - A208T	4.66838	5.456726	6.028038	6.740521	4.368945
D2HGDH - R212W	5.536191	7.573859	6.988648	8.26961	7.989582
D2HGDH - R421H	1.335891	2.469225	2.337813	1.663264	1.389835
D2HGDH - A426T	2.344331	3.82037	2.875458	5.230389	5.053128
D2-HC pmol/mg of protoin - c		roplicatos			
MSCV	26 21722	10 78871	13 83083		
	20.347.33	12 26429	0.20061		
	9.303139	10.50420	9.20001		
	22 00779	16.02090	22.20002		
	23.99770	20.22417	20.30293		
	5.51374	0.497204	7.240000		
D2HGDH - A4261	7.529353	10.59393	7.630245		
L2-HG pmol/mg of protein, 3	replicates				
MSCV	179.3523	113.1284	123.4135		
D2HGDH - WT	141.5041	148.9788	125.1581		
D2HGDH - G131X	125.0785	116.308	109.4466		
D2HGDH - A208T	167.5777	138.9724	155.4484		
D2HGDH - R421H	111.0916	91.20035	92.75989		
D2HGDH - A426T	120.1405	129.3849	106.5934		
2-KG pmol/mg of protein ass	av#1 4 rer	licates			
MSCV	1971.995	2196.937	2416.924	2896 858	
D2HGDH - WT	4719 369	4166 875	3449 139	3894 311	
D2HGDH - G131X	1431 407	1766 205	1333.068	1651 335	
D2HGDH - A208T	1843 989	2075.87	1531 019	1865 886	
D2HGDH - R/21H	1/66 016	1622 627	1058 838	1030 705	
D2HGDH - A426T	2050.196	1964.029	1959.822	2005.751	
	au#0_4_mam	lington			
2-KG pmoi/mg of protein, ass	ay#2, 4 rep	licates			
MSCV	1855.615	1558.616	1744.538	2453.218	
D2HGDH - WI	3999.018	2828.462	2733.508	2423.464	
D2HGDH - G131X	238.939	539.663	480.198	578.263	
D2HGDH - A208T	734.603	1043.636	887.809	1088.109	
D2HGDH - R421H	1420.497	2164.322	1502.578	1198.894	
D2HGDH - A426T	1830.906	1006.023	1047.18	1040.221	
2-KG pmol/mg of protein, ass	ay#3, 5 rep	licates			
MSCV	1025.726	768.7465	776.5064	727.4821	1530.187
D2HGDH - WT	1581.188	763.424	1491.919	1513.157	1188.635
D2HGDH - R212W	740.7486	357.0364	924.6938	297.2062	583.04
D2HGDH transient express	ion cell mo	del			
D2-HG pmol/mg of protein - a	assay#1, 3 i	replicates			
MSCV	36.64416	36.4722	40.08173		
D2HGDH - WT 0.5ug	29.68443	27.44684	32.32854		
D2HGDH - WT 0.75ug	22.03808	23.38029	27.88385		
D2HGDH - WT 1.0ug	14.61641	20.90789	11.17389		
D2-HG pmol/ma of protein - a	assav#2.3	replicates			
MSCV	31.75372	28,76147	36,49974		
D2HGDH - WT 0.5ug	19.03621	21.51516	19.99729		
D2HGDH - WT 0.75ug	16.49129	15.69138	18.33014		
D2HGDH - WT 1.0ug	12.7291	19.3764	13.86678		
.					

2-KG pmol/mg of protein - assay#1, 3 replicates					
MSCV	375.6534	546.3336	671.2131		
D2HGDH - WT 0.5ug	848.2435	655.7721	779.4605		
D2HGDH - WT 0.75ug	803.1845	839.1634	980.6399		
D2HGDH - WT 1.0ug	930.7704	911.0911	893.8879		

2-KG pmol/mg of protein - assay#2, 3 replicates					
MSCV	521.091	507.3479	521.134		
D2HGDH - WT 0.5ug	820.3983	774.3329	696.7507		
D2HGDH - WT 0.75ug	814.7245	885.1288	805.5704		
D2HGDH - WT 1.0ug	845.1482	860.8818	865.4253		

Supplementary Table 12 (continuation)

D2HGDH transient siRNA-KD model

D2-HG pmol/mg	of protein - a	ssay#1, 2 replicates	5
si-RNA ctrl	89.93771	80.97425	
si-RNA D2#5	114.5639	142.3544	
si-RNA D2#3	134.5945	137.5139	
2-KG pmol/mg o	f protein - ass	say#1, 2 replicates	
si-RNA ctrl	313.5986	362.0601	
si-RNA D2#5	238.3543	229.6885	
si-RNA D2#3	206.4567	231.8885	
L2-HG pmol/mg	of protein - a	ssay#1, 2 replicates	
si-RNA ctrl	227.8028	207.9399	
si-RNA D2#5	208.3678	223.5751	
si-RNA D2#3	152.5984	210.5491	

DLBCL cell lines - D2HGDH WT

D2-HG pmol/mg of protein, 3 biological replicates (each representing the mean of technical triplicates)

OCI-Ly1	11.94	4.19	5.49
OCI-Ly4	0.08	0.52	0.59
OCI-Ly18	1.56	1.21	1.31
SU-DHL4	5.99	0.99	0.97
SU-DHL10	18.40	3.62	0.26
SU-DHL2	0.02	0.52	0.10
Farage	0.20	0.62	0.41
OCI-Ly8	16.41	1.12	6.32
OCI-Ly10	0.25	0.75	5.56
OCI-Ly19	8.25	1.28	7.16

2-KG pmol/mg of protein, 3 biological replicates (each representing the mean of technical triplicates)

OCI-Ly1	264.38	1509.22	398.72	
OCI-Ly4	186.97	302.15	234.85	
OCI-Ly18	699.86	1232.28	1070.77	
SU-DHL4	67.70	737.33	607.24	
SU-DHL10	267.42	2265.06	843.83	
SU-DHL2	139.60	270.09	8952.50	
Farage	98.63	331.14	572.42	
OCI-Ly8	81.27	834.09	4894.93	
OCI-Ly10	65.09	205.27	448.81	
OCI-Ly19	1024.32	708.69	832.61	

DLBCL cell lines - D2HGDH mutant

OCI-Ly7

D2-HG pmol/mg of protein, 3 biological replicates (each representing the mean of technical triplicates)WSU-NHL9.840.530.40SU-DHL67.541.321.18SU-DHL812.390.510.64

2-KG pmol/mg of protein, 3 biological replicates (each representing the mean of technical triplicates)

5.40

0.69

WSU-NHL	143.47	330.17	803.20
SU-DHL6	39.79	82.87	585.57
SU-DHL8	171.76	309.72	783.20
OCI-Ly7	339.31	1175.34	102.27

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Supplementary Note 1:

No somatic variants were reported for D2HGDH in four published sequencing studies on DLBCL, accounting for over 200 patients. Below, we detail the potential reasons for these negative findings.

In Pasqualucci et al¹ only 6 DLBCLs (normal and tumour DNA pairs) were examined by wholeexome sequencing. Subsequently, the authors perform targeted re-sequencing of 56 genes (D2HGDH was NOT one of them) in 48 to 105 additional DLBCL biopsies. In that report, the size of the initial cohort, coupled with the low frequency of DH2HGDH mutations and the selection of a restricted list of candidate gene set for the subsequent analysis, likely explain the absence of D2HGDH variants in their DLBCL collection.

Zhang et al² defined their set of significantly mutated genes based on a discovery cohort of 34 paired DLBCL samples. According to their criteria, genes not previously associated with cancer were required to be mutated in at least two samples for inclusion in their list of significant candidates, which would eliminate genes with mutation frequencies lower than 6% (thus including D2HGDH which we found to be mutant in 3.3% of the primary samples or 5.8% primary samples + cell lines). In Zhang et al, the subsequent validation set was only screened for the genes identified in the smaller discovery cohort and thus would not have revealed D2HGDH mutations. Of note, Zhang et al. explored in great detail the degree of overlap between 'DLBCL genes' identified by theirs and the other studies discussed above; they found a surprisingly low concordance among the four studies at all mutation frequency levels, but especially for the genes mutated in at least 10% of the cases in their study were not detected by any of the remaining three studies and concluded that genetic heterogeneity in the disease

might contribute to the observed patterns of disparate mutations. The report on the 21 lymphoma cell lines studied by Zhang et al² is limited to the "322 DLBCL genes" that the authors identified in the initial 34 paired-samples cohort, and that does not include D2HGDH

The design of the study by Morin et al⁵ was powered to pick up mutations at frequencies of 2.8% and higher, which would theoretically be sensitive enough to detect D2HGDH mutations at our estimated frequency of 5.4% (8 mutations in 148 samples – 4 in 120 primary tumors – 3.3%; 4 in 28 DLBCL cell lines 14%). However, in that study coding variants present in the dbSNP were removed at the first step of the analysis. If we apply these criteria to our cohort, 2 variants found in 4 of our primary biopsies (R421H and A426T), would have been excluded, leaving a residual frequency of D2HGDH mutations of 2.7%, which would fall within the margin of error of Morin et al.'s detection. Morin et al. also sequenced 10 DLBCL cell lines, and of those, the only ones that we report as having D2HGDH mutation are SU-DHL-6 and OCI-Ly7. Coincidently, these are exactly the cell lines with the R421H and A426T variants reported in dbSNP, which again would be removed from their analysis. We should indicate here that not only we demonstrated that these variants render D2HGDH inactive, but their frequency in non-malignant tissues (i.e., reference databases) is markedly lower than that of our DLBCL cohort. Finally, as referred to before, the A426T allele has been found to segregate with familial cases of D-2-hydroxyglutaric aciduria, further highlighting its biological relevance.

Lohr et al⁸ studied a cohort of 49 normal and tumour DNA pairs. Although they applied algorithms to recognize significantly mutated genes at low frequency, their sample size would put them right at the limit of detection for D2HGDH variants (3.3% based on 4 D2HGDH mutants in 120 primary tumours in our cohort). In other words, all things being equal, they could find ~ 1.6 tumours mutant for D2HGDH in 49 samples. Importantly, the authors recognize that some mutations that may be functionally relevant would not meet statistical significance based

on their algorithms. In fact, by expanding the scale of their genomic analysis and applying novel

statistical definitions, the same group recognized that current genomic studies have not yet

achieved saturation for cancer gene discovery⁹.

Supplementary References:

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