Supplementary Text 1

1 Data Ascertainment

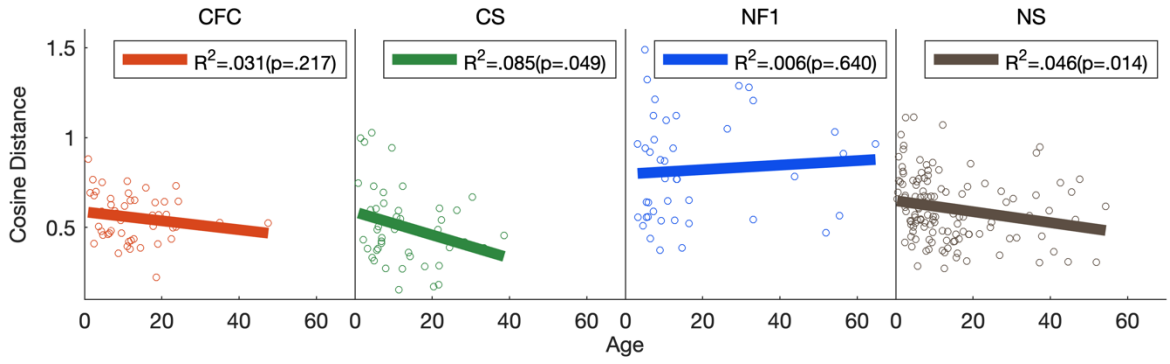
Patients from the FaceBase repository (collection: FB00000861) were recruited at patient meetings and genetics clinics in Colorado, Los Angeles, San Francisco, Stanford, USA and Alberta, Canada. If patients were recruited at a patient meeting, diagnosis was usually self-reported. When patients were seen at a clinic, a clinical diagnosis was established by a clinical geneticist, often followed by molecular confirmation. Patients in the database of the Western Australian Health Department were ascertained through multi-stakeholder (including patient) scientific meetings after individual in person review by a clinical geneticist (author GB) or via clinical geneticists directly from clinical genetics services. Patients in Peter Hammond's collection were recruited at patient support groups across the United States, UK and Italy. At initial recruitment, diagnosis was recorded as reported by families or suggested by clinical geneticists attending the meetings; some patients were in contact over several years and molecular diagnoses were reported by parents or by collaborating clinical geneticists.

2 Age-related changes to variation and similarity statistics

In the main text we use facial signatures to describe each patient. These represent how each patient differs from an age- and sex- appropriate normal reference population. Using facial signatures adjusts for the effects of normal growth and development on the face. However, age-related changes due to abnormal growth (such as the gradual appearance of syndrome-specific features) may still occur and these can affect the statistics presented in this paper. In this section we investigate these changes in the sample of RASopathies.

2.1 Age-related changes to directional variation

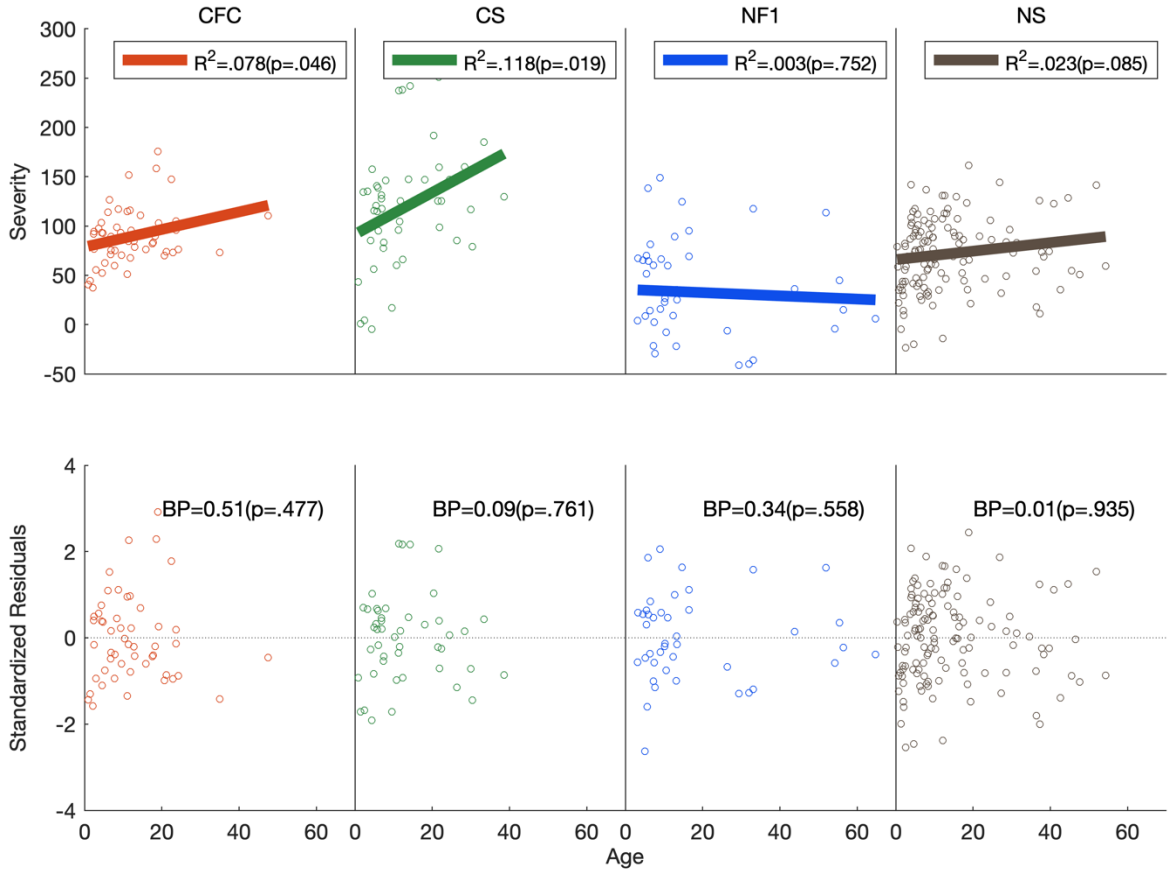
Directional variation is defined as the central tendency of the distribution of cosine distances from the mean signature. To investigate age-related changes to directional variation we regressed cosine distance to the mean signature onto age within each of the four syndromes. This was done using ordinary least-squares regression. The results are shown in Supplementary Text Figure 1. The regressions within CS and NS were significant suggesting that directional variation declines with age in these syndromes.



Supplementary Text Figure 1. Age-related changes to the directional variation statistic. In general cosine distance to the mean signature declines with age in CS and NS.

2.2 *Age-related changes to severity and severity variation*

We assessed age-related changes to severity via ordinary least-squares regression of severity onto age. Severity variation is the dispersion of severity scores from their central tendency. To assess age-related changes to severity variation we tested for changes to the dispersion relative to the linear regression (i.e. the dispersion of the residuals of the regression) using the Breusch-Pagan test for heteroscedasticity. Results are shown Supplementary Text Figure 2. CFC and CS become more severe with age. There is no evidence of heteroscedasticity for any of the syndromes and thus no evidence for age-related changes in severity variation.



Supplementary Text Figure 2. Age-related changes in severity and severity variation. The top row plots the linear regression of severity onto age. CFC and CS become more severe with age. The bottom row plots the standardized residuals of each regression. BP denotes the Breusch-Pagan statistic.

2.3 *Age-related changes to the typical phenotype and the phenotype agreement statistics*

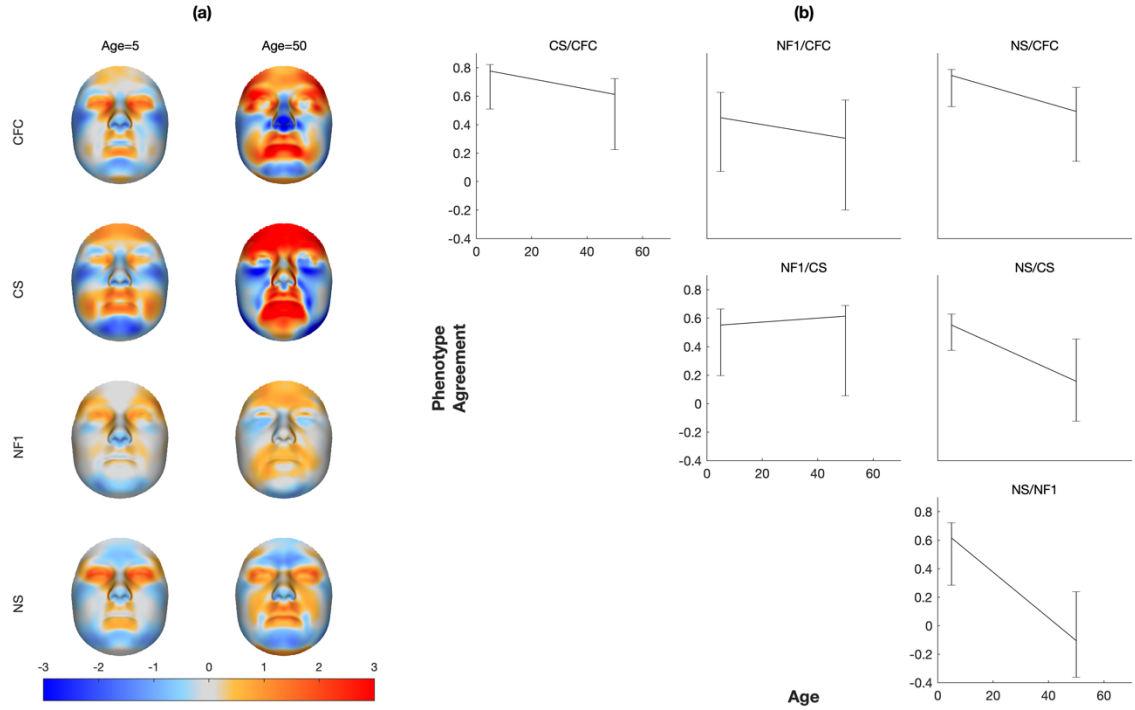
Age-related changes to phenotype agreement were assessed by firstly modelling the age-related change in the facial signatures for each syndrome. This was approximated using a multivariate linear partial least-squares regression of the signatures onto age. This fits the model:

$$\hat{Y} = MX + C$$

Where $\hat{Y}$ denotes the matrix of fitted values (expected signatures), M denotes the matrix of regression coefficients, X denotes the matrix of predictors (in this case only age), and C denotes the matrix of constant values. A model was fitted separately for each syndrome and statistical significance was evaluated using a permutation test on the variance explained (R^2) as per Shrimpton et al. [1]. The regressions were also evaluated at ages 5 and 50, yielding

expected signatures for each age for each syndrome. As these result from the imposition of a linear model, where changes would in fact be expected be non-linear, these should not be taken as exact age-specific estimates of the typical phenotype. Nevertheless, comparing the expected signatures at different ages can reveal the general trend of changes in the phenotype. For calculating phenotype agreement and statistical significance we used as signatures feature vectors combining signatures in the x y and z direction, as were used as the basis for all statistical analysis in this article. For illustrating the expected signatures we fitted separate models regressing the signatures in the direction normal to the surface onto age.

For illustration, the expected signatures in the direction normal to the surface are shown in Supplementary Text Figure 3 part (a). The regressions for CS (R^2=.070; p<.001) and NS (R^2=.020; p=.003) were significant. In general, the trend in CS is for features to become more extreme (the colors become deeper) consistent with the age-related change in severity observed in section 2.2 above. The submalar and mandibular portion of the cheeks also become less prominent (this region goes from being orange to light blue). In NS the prominence of the lips increases (this region becomes redder). The forehead and chin become bluer consistent with increased retrusion of the forehead and increased micrognathia. The middle malar and submalar regions of the cheeks become more prominent (redder). The regressions for CFC (R^2=.031; p=.109) and NF1 were non-significant (R^2=.019; p=.641).

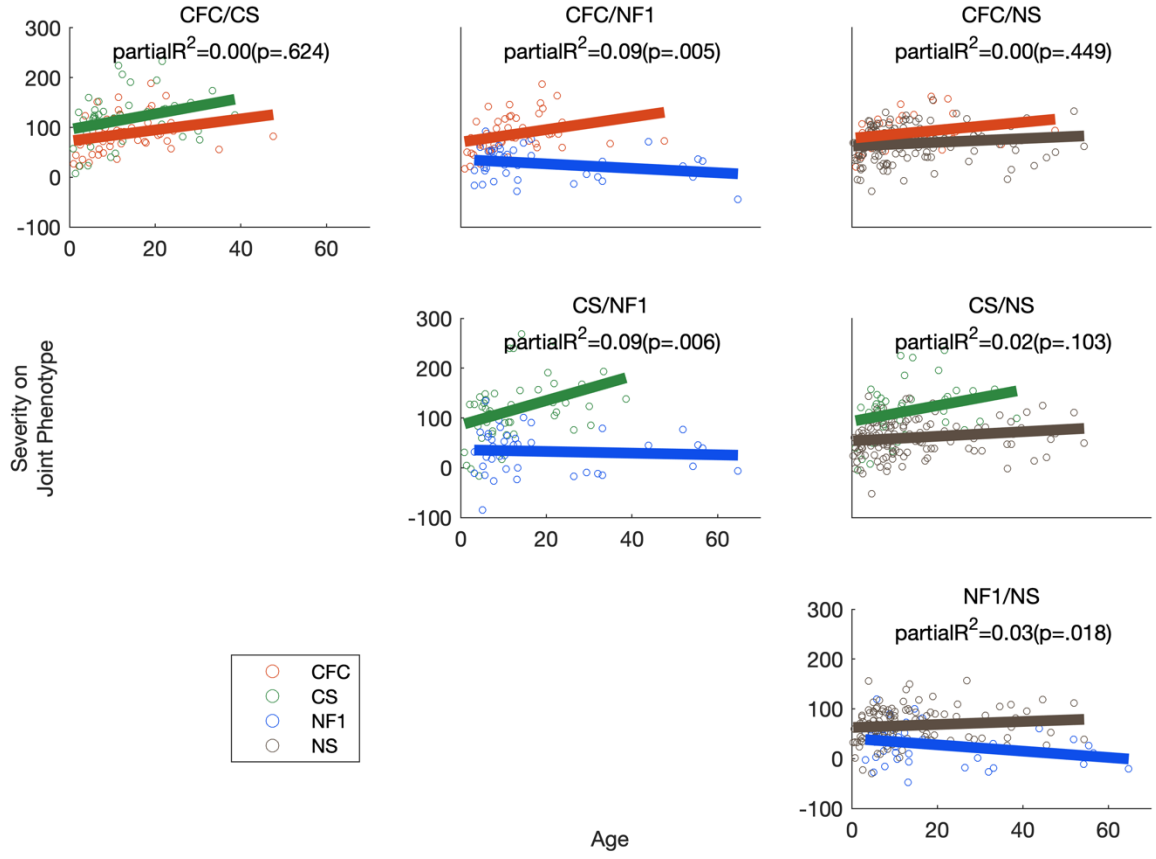


Supplementary Text Figure 3. Age-related changes in the typical phenotype and changes in the phenotype agreement statistic. Part (a) plots the expected signature at ages 5 and 50 predicted by a linear regression of the signatures in the direction normal to the facial surface (red indicates outward displacement, blue indicates inward displacement). Part (b) plots the expected changes in the phenotype agreement statistic as a result of the changes in the typical phenotype. 95% confidence intervals were calculated by resampling the data within each syndrome with replacement 1000 times, refitting the models and revaluating the expected signatures and phenotype agreement.

To assess how these changes affect the phenotype agreement statistic the phenotype agreement (cosine) between corresponding pairs of expected signatures was calculated. For example, to estimate the phenotype agreement between CS and NS at age 5 the cosine

between the expected signatures for CS at age 5 and for NS at age 5 was computed. Comparing the phenotype agreement at age 5 to age 50 reveals the general trend of how age-related changes in the phenotype influence the phenotype agreement statistic. These trends are plotted in Supplementary Text Figure 3 part (b). In general, the trend is for each syndrome to become more distinct (phenotype agreement decreases between all pairs of syndromes except NF1 and CS). The largest divergence is between NS and NF1 and NS and CS.

2.4 Age-related changes to severity differences



Supplementary Text Figure 4. Age-related changes to severity difference statistics. Each panel plots the severity scores along a combined phenotype for a particular pair of syndromes as a function of age. This is annotated with the linear regressions of age onto severity computed separately for each group. Text labels show the partial R^2 and p value associated with the interaction term of the corresponding general linear model (see text) and indicate the significance of the differences between regression slopes.

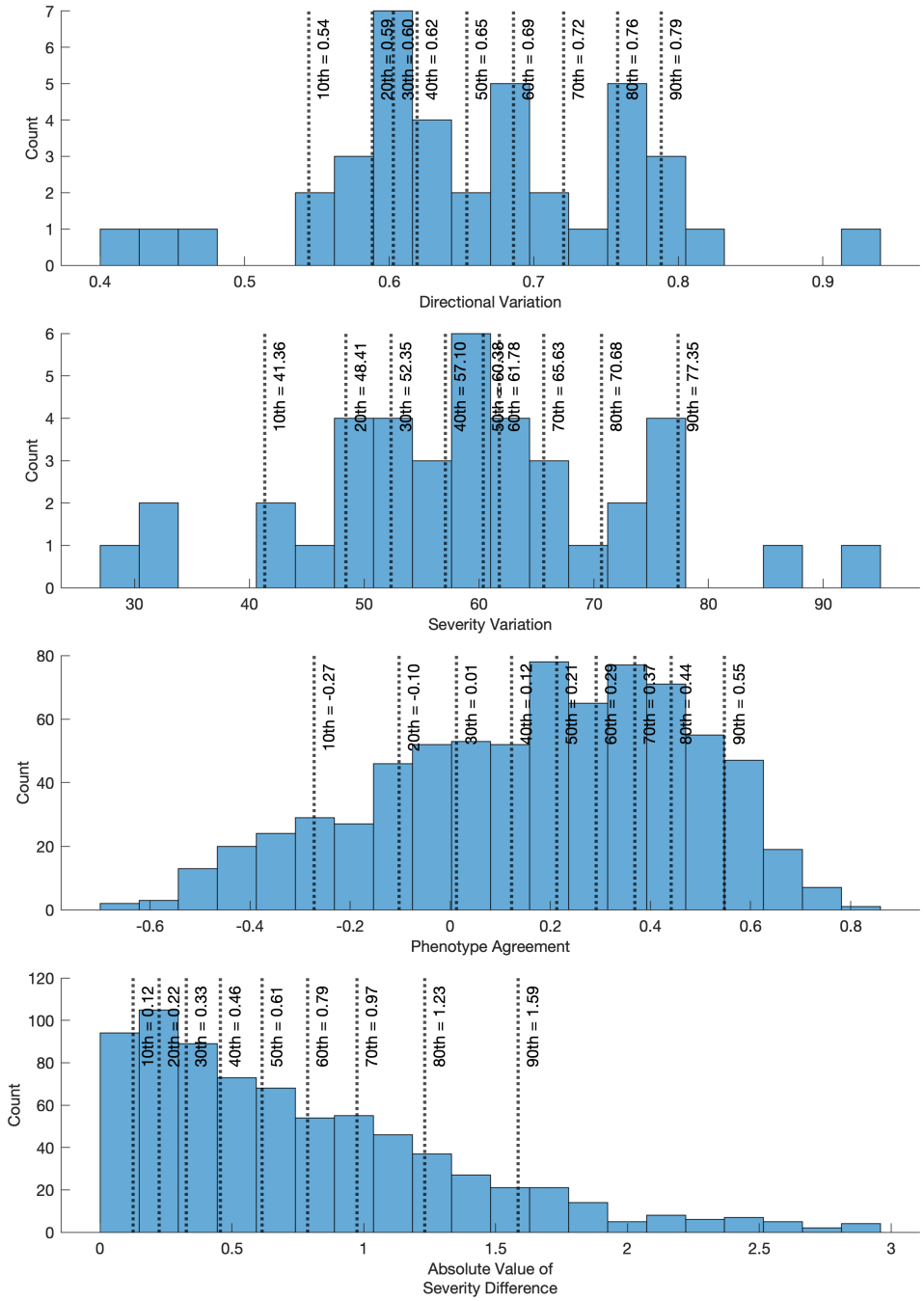
Severity difference is the difference between the central tendencies of the distributions of severity scores (expressed as Cohen's D statistic) of two syndromes. For calculating severity difference, severity is calculated with respect to the combined typical phenotype of both syndromes (estimated as the mean of the two mean signatures of the syndromes separately). This is done to jointly ordinate both syndromes on a common axis. To assess age-related changes in severity difference between each pair of syndromes we compare the slopes of linear regressions of these severity scores for each syndrome. This was done for each pair of syndromes by fitting a general linear model consisting of a main effect of syndrome (with two levels corresponding to the two syndromes in question), a main effect of age and a syndrome*age interaction. A significant interaction term indicates the slopes of the

regressions of age on severity differ between the two groups and that the difference in severity is either increasing or decreasing. Results are plotted in Supplementary Text Figure 4. For NF1 paired with CFC and CS and NF1 paired with NS the interaction is significant indicating that severity difference increases with age between these pairs of syndromes.

References

1 Shrimpton S, Daniels K, De Greef S, Tilotta F, Willems G, Vandermeulen D, Suetens P, Claes P. A spatially-dense regression study of facial form and tissue depth: Towards an interactive tool for craniofacial reconstruction. *Forensic Science International* 2014;**234**:103–10.

Supplementary Figures



Supplementary Figure 1. Distributions of the directional variation, severity variation, phenotype agreement and severity difference statistics computed from the sample of disorders described in Supplementary Table 2.

Supplementary Tables

Supplementary Table 1. Image exclusion criteria. This shows the numbers remaining in each sample after each successive exclusion criterion was applied. Images were excluded due to 1) poor image quality including non-neutral facial expression, 2) missing data on age and sex or ethnicity, 3) failed image registration, 4) being a duplicate image of a patient already included in the analysis and 5) non-European ancestry. The final row, therefore, shows final numbers after all exclusion criteria were applied.

	CFC	CS	NF1	NS
INITIAL NUMBERS	76	77	94	174
POOR IMAGE QUALITY	62	60	87	161
MISSING DEMOGRAPHIC DATA	57	54	60	143
REGISTRATION FAILED	54	47	58	139
DUPLICATE PATIENT	54	46	55	132
NON-EUROPEAN ANCESTRY	51	46	42	129

Supplementary Table 2. Age, sex, clinical, and, where available, molecular diagnoses for each participant. Where available the molecular diagnosis at the gene, DNA and protein level as well as the variant's American College of Medical Genetics (ACMG) classification is reported.

Patient Study ID	Age (years)	Sex	Diagnosis	Molecular confirmation available	Gene	DNA	Protein	ACMG classification
CFC001	12.1	M	Cardiofaciocutaneous syndrome	Yes	MEK2			
CFC002	19.2	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC003	2.2	M	Cardiofaciocutaneous syndrome	No				
CFC004	2.5	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC005	1.5	F	Cardiofaciocutaneous syndrome	No				
CFC006	11.4	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC007	17.8	F	Cardiofaciocutaneous syndrome	No				
CFC008	9.4	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC009	3.7	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC010	4.6	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC011	7.8	F	Cardiofaciocutaneous syndrome	Yes	MEK1			
CFC012	4.4	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC013	19.0	F	Cardiofaciocutaneous syndrome	Yes	MEK1			
CFC014	6.5	F	Cardiofaciocutaneous syndrome	No				
CFC015	11.8	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC016	11.1	M	Cardiofaciocutaneous syndrome	No				
CFC017	15.9	F	Cardiofaciocutaneous syndrome	Yes	MEK1			
CFC018	6.9	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC019	7.9	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC020	8.8	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.770A>G	p.Gln257Arg	Pathogenic
CFC021	18.3	F	Cardiofaciocutaneous syndrome	No				
CFC022	20.7	M	Cardiofaciocutaneous syndrome	Yes	MAP2K1	c.389A>G	p.Tyr130Cys	Pathogenic
CFC023	22.8	M	Cardiofaciocutaneous syndrome	No				
CFC024	9.6	M	Cardiofaciocutaneous syndrome	No				

CFC025	6.1	M	Cardiofaciocutaneous syndrome	No				
CFC026	4.8	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.1787G>T	p.Gly596Val	Pathogenic
CFC027	24.3	F	Cardiofaciocutaneous syndrome	No				
CFC028	6.8	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC029	11.4	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.770A>G	p.Gln257Arg	Pathogenic
CFC030	11.9	M	Cardiofaciocutaneous syndrome	Yes	BRAF	c.1787G>T	p.Gly596Val	Pathogenic
CFC031	23.7	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC032	0.9	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.1497A>C	p.Lys499Asn	Pathogenic
CFC033	6.8	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.1406G>A	p.Gly469Glu	Pathogenic
CFC034	3.0	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC035	17.6	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC036	13.0	M	Cardiofaciocutaneous syndrome	Yes	MAP2K1	c.389A>G	p.Tyr130Cys	Pathogenic
CFC037	22.5	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC038	14.5	M	Cardiofaciocutaneous syndrome	Yes	MAP2K2	c.395G>A	p.Gly132Asp	Likely Pathogenic
CFC039	18.6	F	Cardiofaciocutaneous syndrome	No				
CFC040	8.4	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC041	4.5	M	Cardiofaciocutaneous syndrome	No				
CFC042	12.8	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC043	2.4	M	Cardiofaciocutaneous syndrome	No				
CFC044	11.1	F	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC045	10.4	F	Cardiofaciocutaneous syndrome	No				
CFC046	21.2	F	Cardiofaciocutaneous syndrome	No				
CFC047	23.7	F	Cardiofaciocutaneous syndrome	No				
CFC048	47.6	M	Cardiofaciocutaneous syndrome	Yes	BRAF			
CFC049	35.0	F	Cardiofaciocutaneous syndrome	Yes	BRAF	c.1787G>T	p.Gly596Val	Pathogenic
CFC050	2.5	F	Cardiofaciocutaneous syndrome	No				
CFC051	5.3	M	Cardiofaciocutaneous syndrome	No				

Costello001	0.9	F	Costello syndrome	Yes	HRAS			
Costello002	11.4	F	Costello syndrome	No				
Costello003	10.3	M	Costello syndrome	No				
Costello004	4.5	M	Costello syndrome	Yes	HRAS			
Costello005	12.3	F	Costello syndrome	Yes	HRAS			
Costello006	11.8	F	Costello syndrome	Yes	HRAS			
Costello007	26.4	M	Costello syndrome	Yes	HRAS			
Costello008	24.5	M	Costello syndrome	Yes	HRAS			
Costello009	22.4	M	Costello syndrome	Yes	HRAS			
Costello010	5.8	F	Costello syndrome	Yes	HRAS			
Costello011	21.8	F	Costello syndrome	Yes	HRAS			
Costello012	18.1	F	Costello syndrome	Yes	HRAS			
Costello013	21.5	M	Costello syndrome	Yes	HRAS			
Costello014	5.7	M	Costello syndrome	Yes	HRAS			
Costello015	21.9	F	Costello syndrome	Yes	HRAS			
Costello016	13.9	F	Costello syndrome	Yes	HRAS			
Costello017	11.6	F	Costello syndrome	Yes	HRAS			
Costello018	33.4	F	Costello syndrome	No				
Costello019	6.8	F	Costello syndrome	Yes	HRAS	c.34G>T	p.Gly12Cys	Pathogenic
Costello020	20.3	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello021	5.0	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello022	7.9	F	Costello syndrome	Yes	HRAS	c.37G>T	p.Gly13Cys	Pathogenic
Costello023	30.0	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello024	4.3	F	Costello syndrome	Yes	HRAS	c.37G>T	p.Gly13Cys	Pathogenic
Costello025	14.3	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello026	30.4	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello027	5.9	F	Costello syndrome	Yes	HRAS	c.34G>T	p.Gly12Cys	Pathogenic

Costello028	38.6	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello029	6.9	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello030	1.4	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello031	21.7	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello032	4.9	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello033	2.2	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello034	11.2	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello035	4.0	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello036	7.4	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello037	9.6	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello038	6.1	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello039	3.2	F	Costello syndrome	No				
Costello040	12.4	F	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello041	5.4	F	Costello syndrome	Yes	HRAS	c.34G>T	p.Gly12Cys	Pathogenic
Costello042	6.8	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello043	2.4	F	Costello syndrome	Yes	HRAS	c.37G>T	p.Gly13Cys	Pathogenic
Costello044	7.4	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello045	28.4	M	Costello syndrome	Yes	HRAS	c.34G>A	p.Gly12Ser	Pathogenic
Costello046	10.7	M	Costello syndrome	Yes	HRAS	c.37G>T	p.Gly13Cys	Pathogenic
NF001	13.4	M	Neurofibromatosis type 1	Yes	NF1	c.7954C>T	p.Gln2652Ter	Pathogenic
NF002	7.7	M	Neurofibromatosis type 1	Yes	NF1			
NF003	13.3	F	Neurofibromatosis type 1	No				
NF004	3.3	M	Neurofibromatosis type 1	No				
NF005	54.3	F	Neurofibromatosis type 1	No				
NF006	10.6	M	Neurofibromatosis type 1	No				
NF007	51.9	F	Neurofibromatosis type 1	No				
NF008	16.5	M	Neurofibromatosis type 1	Yes	NF1	c.1466A>G	p.Tyr489Cys	Pathogenic

NF009	10.2	M	Neurofibromatosis type 1	No				
NF010	12.8	F	Neurofibromatosis type 1	Yes	NF1	Deletion exons 39-45		Pathogenic
NF011	7.5	F	Neurofibromatosis type 1	No				
NF012	9.3	F	Neurofibromatosis type 1	No				
NF013	10.9	F	Neurofibromatosis type 1	No				
NF014	12.3	M	Neurofibromatosis type 1	No				
NF015	5.5	M	Neurofibromatosis type 1	Yes	NF1	c.1756_1759del	p.Thr586ValfsTer18	Pathogenic
NF016	7.3	F	Neurofibromatosis type 1	No				
NF017	5.8	F	Neurofibromatosis type 1	Yes	NF1	Microdeletion		Pathogenic
NF018	9.1	F	Neurofibromatosis type 1	Yes	NF1	c.3457_3460del	p.Leu1153fsMetfsTer4	Pathogenic
NF019	13.2	M	Neurofibromatosis type 1	No				
NF020	4.6	F	Neurofibromatosis type 1	Yes	NF1	c.7031del	p.Asn2344IlefsTer31	Pathogenic
NF021	16.5	F	Neurofibromatosis type 1	Yes	NF1			
NF022	6.4	M	Neurofibromatosis type 1	No				
NF023	3.2	M	Neurofibromatosis type 1	No				
NF024	5.5	F	Neurofibromatosis type 1	No				
NF025	5.2	M	Neurofibromatosis type 1	No				
NF026	6.0	F	Neurofibromatosis type 1	Yes	NF1	c.3938_3942del	p.Asp1313AlafsTer4	Pathogenic
NF027	8.9	M	Neurofibromatosis type 1	No				
NF028	33.1	M	Neurofibromatosis type 1	No				
NF029	56.5	F	Neurofibromatosis type 1	No				
NF030	10.3	M	Neurofibromatosis type 1	No				
NF031	6.3	F	Neurofibromatosis type 1	No				
NF032	64.8	F	Neurofibromatosis type 1	No				
NF033	7.3	F	Neurofibromatosis type 1	No				
NF034	26.4	F	Neurofibromatosis type 1	Yes	NF1	c.1019_1020del	p.Ser340CysfsTer12	Pathogenic
NF035	55.4	F	Neurofibromatosis type 1	No				

NF036	43.8	F	Neurofibromatosis type 1	No				
NF037	32.0	F	Neurofibromatosis type 1	No				
NF038	33.1	M	Neurofibromatosis type 1	No				
NF039	14.7	M	Neurofibromatosis type 1	No				
NF040	29.4	M	Neurofibromatosis type 1	No				
NF041	5.7	F	Neurofibromatosis type 1	No				
NF042	5.1	M	Neurofibromatosis type 1	Yes	NF1	c.4105del	p.Tyr1369ThrfsTer16	Pathogenic
Noonan001	2.4	M	Noonan syndrome	No				
Noonan002	28.6	F	Noonan syndrome	Yes	PTPN11			
Noonan003	14.9	M	Noonan syndrome	Yes	RAF1			
Noonan004	5.0	F	Noonan syndrome	Yes	NRAS			
Noonan005	9.0	M	Noonan syndrome	No				
Noonan006	4.0	M	Noonan syndrome	No				
Noonan007	46.5	M	Noonan syndrome	No				
Noonan008	47.6	F	Noonan syndrome	Yes	PTPN11			
Noonan009	7.4	M	Noonan syndrome	No				
Noonan010	13.2	M	Noonan syndrome	Yes	PTPN11			
Noonan011	40.9	F	Noonan syndrome	Yes	PTPN11			
Noonan012	16.5	F	Noonan syndrome	No				
Noonan013	12.6	M	Noonan syndrome	No				
Noonan014	5.0	F	Noonan syndrome	No				
Noonan015	37.2	F	Noonan syndrome	No				
Noonan016	5.2	F	Noonan syndrome	No				
Noonan017	18.6	M	Noonan syndrome	No				
Noonan018	7.1	F	Noonan syndrome	No				
Noonan019	38.3	F	Noonan syndrome	No				
Noonan020	1.2	F	Noonan syndrome	Yes	PTPN11			

Noonan021	2.0	M	Noonan syndrome	No	
Noonan022	7.9	M	Noonan syndrome	No	
Noonan023	5.3	M	Noonan syndrome	No	
Noonan024	45.5	M	Noonan syndrome	No	
Noonan025	6.0	F	Noonan syndrome	Yes	PTPN11
Noonan026	7.6	M	Noonan syndrome	No	
Noonan027	8.3	M	Noonan syndrome	No	
Noonan028	6.3	M	Noonan syndrome	Yes	PTPN11
Noonan029	37.3	F	Noonan syndrome	Yes	PTPN11
Noonan030	7.2	M	Noonan syndrome	No	
Noonan031	5.1	M	Noonan syndrome	Yes	BRAF
Noonan032	0.8	M	Noonan syndrome	No	
Noonan033	19.0	F	Noonan syndrome	Yes	PTPN11
Noonan034	8.4	M	Noonan syndrome	No	
Noonan035	8.4	M	Noonan syndrome	No	
Noonan036	2.7	M	Noonan syndrome	Yes	PTPN11
Noonan037	5.9	F	Noonan syndrome	No	
Noonan038	5.6	F	Noonan syndrome	No	
Noonan039	11.8	F	Noonan syndrome	No	
Noonan040	23.1	M	Noonan syndrome	No	
Noonan041	17.5	M	Noonan syndrome	No	
Noonan042	28.6	F	Noonan syndrome	No	
Noonan043	10.1	M	Noonan syndrome	No	
Noonan044	11.2	F	Noonan syndrome	No	
Noonan045	37.8	M	Noonan syndrome	No	
Noonan046	2.5	F	Noonan syndrome	No	
Noonan047	8.7	F	Noonan syndrome	No	

Noonan048	42.6	M	Noonan syndrome	No	
Noonan049	0.6	M	Noonan syndrome	No	
Noonan050	13.5	F	Noonan syndrome	No	
Noonan051	16.0	F	Noonan syndrome	Yes	PTPN11
Noonan052	12.7	M	Noonan syndrome	Yes	PTPN11
Noonan053	4.6	M	Noonan syndrome	No	
Noonan054	10.0	F	Noonan syndrome	No	
Noonan055	4.5	M	Noonan syndrome	No	
Noonan056	29.5	M	Noonan syndrome	No	
Noonan057	16.0	M	Noonan syndrome	No	
Noonan058	8.2	M	Noonan syndrome	No	
Noonan059	2.6	M	Noonan syndrome	No	
Noonan060	44.6	F	Noonan syndrome	No	
Noonan061	19.5	M	Noonan syndrome	Yes	PTPN11
Noonan062	2.4	F	Noonan syndrome	Yes	PTPN11
Noonan063	4.5	M	Noonan syndrome	No	
Noonan064	5.7	M	Noonan syndrome	No	
Noonan065	10.0	F	Noonan syndrome	No	
Noonan066	7.4	M	Noonan syndrome	No	
Noonan067	7.4	M	Noonan syndrome	No	
Noonan068	1.8	F	Noonan syndrome	No	
Noonan069	39.7	M	Noonan syndrome	No	
Noonan070	9.4	M	Noonan syndrome	No	
Noonan071	2.0	F	Noonan syndrome	No	
Noonan072	1.9	M	Noonan syndrome	Yes	PTPN11
Noonan073	2.4	M	Noonan syndrome	Yes	PTPN11
Noonan074	1.7	M	Noonan syndrome	Yes	PTPN11

Noonan075	3.1	M	Noonan syndrome	No				
Noonan076	6.4	M	Noonan syndrome	No				
Noonan077	12.1	M	Noonan syndrome	Yes	PTPN11			
Noonan078	30.4	F	Noonan syndrome	Yes	SOS1			
Noonan079	0.8	F	Noonan syndrome	Yes	SOS1			
Noonan080	14.9	F	Noonan syndrome	Yes	PTPN11	c.922A>G	p.Asn308Asp	Pathogenic
Noonan081	18.4	M	Noonan syndrome	No				
Noonan082	6.5	M	Noonan syndrome	Yes	PTPN11	c.1472C>A	p.Pro491His	Pathogenic
Noonan083	5.9	F	Noonan syndrome	Yes	PTPN11	c.1510A>G	p.Met504Val	Pathogenic
Noonan084	5.5	F	Noonan syndrome	Yes	PTPN11	c.922A>G	p.Asn308Asp	Pathogenic
Noonan085	31.3	F	Noonan syndrome	Yes	PTPN11	c.922A>G	p.Asn308Asp	Pathogenic
Noonan086	17.5	M	Noonan syndrome	Yes	PTPN11	c.922A>G	p.Asn308Asp	Pathogenic
Noonan087	5.0	F	Noonan syndrome	No				
Noonan088	2.1	M	Noonan syndrome	No				
Noonan089	1.3	F	Noonan syndrome	Yes	PTPN11	c.802G>T	p.Gly268Cys	Pathogenic
Noonan090	19.3	M	Noonan syndrome	Yes	PTPN11			
Noonan091	51.9	F	Noonan syndrome	Yes	PTPN11	c.317A>C	p.Asp106Ala	Pathogenic
Noonan092	36.4	F	Noonan syndrome	No				
Noonan093	21.7	F	Noonan syndrome	No				
Noonan094	17.2	F	Noonan syndrome	Yes	PTPN11	c.417G>C	p.Glu139Asp	Pathogenic
Noonan095	8.3	M	Noonan syndrome	Yes	RAF1			
Noonan096	13.5	F	Noonan syndrome	Yes	PTPN11			
Noonan097	18.9	M	Noonan syndrome	Yes	PTPN11			
Noonan098	3.8	M	Noonan syndrome	Yes	PTPN11	c.923A>G	p.Asn308Ser	Pathogenic
Noonan099	9.6	M	Noonan syndrome	Yes	PTPN11			
Noonan100	15.3	F	Noonan syndrome	Yes	PTPN11	c.1403C>T	p.Thr468Met	Pathogenic
Noonan101	3.9	M	Noonan syndrome	Yes	PTPN11			

Noonan102	0.3	F	Noonan syndrome	Yes	PTPN11			
Noonan103	34.6	F	Noonan syndrome	No				
Noonan104	8.6	M	Noonan syndrome	Yes	PTPN11	c.1471C>T	p.Pro491Ser	Pathogenic
Noonan105	9.2	F	Noonan syndrome	No				
Noonan106	16.4	F	Noonan syndrome	Yes	PTPN11			
Noonan107	15.6	M	Noonan syndrome	Yes	PTPN11			
Noonan108	10.3	M	Noonan syndrome	Yes	PTPN11			
Noonan109	6.4	M	Noonan syndrome	Yes	PTPN11			
Noonan110	27.3	F	Noonan syndrome	Yes	PTPN11			
Noonan111	9.6	M	Noonan syndrome	Yes	SOS1	c.1654A>G	p.Arg552Gly	Pathogenic
Noonan112	36.3	F	Noonan syndrome	Yes	SOS1	c.1654A>G	p.Arg552Gly	Pathogenic
Noonan113	26.9	F	Noonan syndrome	No				
Noonan114	24.8	M	Noonan syndrome	Yes	SOS1			
Noonan115	24.5	F	Noonan syndrome	Yes	RAF1			
Noonan116	12.2	M	Noonan syndrome	Yes	PTPN11			
Noonan117	15.7	M	Noonan syndrome	Yes	SOS1			
Noonan118	4.2	M	Noonan syndrome	Yes	PTPN11			
Noonan119	9.7	F	Noonan syndrome	Yes	SHOC2	c.4A>G	p.Ser2Gly	Pathogenic
Noonan120	9.7	F	Noonan syndrome	Yes	SHOC2	c.4A>G	p.Ser2Gly	Pathogenic
Noonan121	17.7	F	Noonan syndrome	Yes	SOS1	c.1859A>G	p.Asp.620Gly	Likely Pathogenic
Noonan122	54.3	F	Noonan syndrome	Yes	SOS1	c.1310T>C	p.Ile437Thr	Pathogenic
Noonan123	3.9	F	Noonan syndrome	Yes	PTPN11	c.184T>G	p.Tyr62Asp	Pathogenic
Noonan124	4.7	M	Noonan syndrome	Yes	CBL	c.1477C>T	p.Leu493Phe	Uncertain Significance
Noonan125	8.0	F	Noonan syndrome	Yes	PTPN11	c.1403C>T	p.Thr468Met	Pathogenic
Noonan126	6.7	M	Noonan syndrome	Yes	PTPN11	c.1403C>T	p.Thr468Met	Pathogenic
Noonan127	13.0	M	Noonan syndrome	Yes	PTPN11	c.1403C>T	p.Thr468Met	Pathogenic
Noonan128	12.1	M	Noonan syndrome	Yes	SOS1	c.1310T>C	p.Ile437Thr	Pathogenic

Noonan129	5.8	M	Noonan syndrome	No

Supplementary Table 3. Samples used to calculate the distributions of the directional variation, severity variation, phenotype agreement and severity difference statistics shown in Supplementary Figure 1. The sample contains only patients of European ancestry. It is known that in the portion of the data coming from the Peter Hammond collection images of the same participant, taken at multiple times, were not always linked by a consistent subject ID. As such this data (although not the RASopathy sample) may contain duplicate images of the same subjects.

Condition	N(Female)	Age Median (IQR)
22q11.2 Del	146(71)	9.25(7.70)
5p Del Cri du Chat	61(34)	13.03(15.90)
Achondroplasia	46(29)	16.28(23.17)
Alstrom	40(19)	23.85(17.60)
Angelman	100(49)	8.15(8.57)
Bardet Biedl	81(40)	24.50(22.92)
CHARGE	89(48)	13.16(11.23)
Cleft Lip Palate	76(27)	9.39(6.12)
Cockayne	33(15)	10.64(9.58)
Cohen	27(15)	18.58(15.75)
Cornelia de Lange	169(91)	11.03(11.59)
Trisomy 21	86(47)	19.71(17.00)
Ectodermal Dysplasia	59(16)	9.80(10.00)
Ehlers Danlos	86(73)	28.42(32.40)
Fabry	35(15)	35.80(26.10)
Fibrodysplasia Ossificans Progressiva	50(28)	18.90(11.90)
Fragile X	62(20)	14.95(17.40)
Galactosemia	38(21)	18.65(18.40)
Jacobsen	53(33)	10.60(9.80)
Joubert	46(21)	8.14(8.90)
Klinefelter	39(0)	16.65(8.60)
Loeys Dietz	62(38)	19.94(21.47)
Marfan	84(54)	20.79(22.82)
Mucopolysaccharidosis	47(22)	18.65(12.42)
Pallister Killian	23(7)	7.22(7.40)
Phelan McDermid	37(16)	9.46(11.20)
Pitt Hopkins	25(15)	8.56(8.41)
Prader Willi	87(43)	15.40(21.70)
Pseudoachondroplasia	25(11)	24.42(26.75)
Rett	45(43)	11.30(8.70)
Rubinstein Taybi	57(30)	9.75(12.40)
Russell Silver	31(8)	7.11(5.43)
Smith Magenis	112(60)	12.40(11.50)
Sotos	37(18)	15.00(11.67)
Stickler	25(16)	20.25(27.08)
Trisomy 18	20(17)	4.70(14.43)
Turner	76(76)	17.84(25.40)
Williams	198(93)	13.50(19.70)
Wolf Hirschhorn	132(73)	7.40(8.50)

Supplementary Table 4. Percentiles of the directional variation, severity variation, phenotype agreement and severity difference statistics computed from the sample of disorders described in Supplementary Table 1.

Percentile	Directional Variation	Severity Variation	Phenotype Agreement	Absolute Value of Severity Difference
1	0.404999599	28.92045205	-0.52858594	0.016847016
2	0.41691339	29.69415697	-0.485725252	0.021956743
3	0.433507598	30.7718174	-0.445224629	0.031892556
4	0.448709565	31.80459449	-0.425861184	0.043587749
5	0.456254203	32.59051316	-0.400588616	0.050268766
6	0.46379884	33.37643182	-0.353876627	0.070652875
7	0.484689684	35.45224114	-0.339692853	0.091097979
8	0.514864846	38.42536568	-0.318528068	0.101799021
9	0.544270101	41.32330631	-0.301932579	0.112765583
10	0.544418946	41.36425794	-0.272389088	0.124896126
11	0.544567791	41.40520958	-0.246851531	0.130653152
12	0.549794209	42.42365033	-0.233848096	0.141251409
13	0.560944463	44.58249504	-0.206593641	0.157235544
14	0.572094716	46.74133976	-0.189189947	0.160257308
15	0.574371473	47.32777583	-0.175639719	0.1691268
16	0.575634115	47.73450807	-0.153246915	0.179394117
17	0.577545298	48.04556819	-0.137678098	0.190353735
18	0.58075356	48.16528408	-0.127254361	0.200124617
19	0.583961823	48.28499997	-0.119635721	0.214921595
20	0.58826769	48.40684978	-0.102030942	0.224104632
21	0.592902839	48.52933976	-0.092151505	0.235993994
22	0.596618194	48.62921088	-0.077809264	0.247289468
23	0.596769349	48.64143392	-0.06651491	0.257490421
24	0.596920503	48.65365696	-0.054163178	0.272063147
25	0.597867259	49.46089825	-0.043292773	0.279704625
26	0.599259551	50.71334978	-0.025370132	0.287243384
27	0.600590289	51.87781068	-0.014045098	0.298807062
28	0.601182369	51.98638412	-0.006242112	0.308058208
29	0.601774449	52.09495756	0.000322494	0.316834715
30	0.60286507	52.34537563	0.012634634	0.32727041
31	0.604429303	52.7305461	0.024875947	0.33640357
32	0.605993536	53.11571657	0.034724832	0.351132668
33	0.608881173	53.41453815	0.042863877	0.368565002
34	0.611840345	53.70869223	0.05612422	0.375131549
35	0.613835775	53.97945631	0.068660436	0.39415268
36	0.61428922	54.2127964	0.07463783	0.404921783
37	0.614742664	54.44613649	0.086679864	0.420028861
38	0.615680065	55.31488247	0.096996213	0.432109909
39	0.616723331	56.32262349	0.113122373	0.445920564
40	0.619354165	57.09764799	0.12264453	0.456350037
41	0.626588942	57.19779458	0.135664084	0.470895852
42	0.633823718	57.29794117	0.147722802	0.494885555
43	0.636096646	57.56437	0.156544542	0.514116247
44	0.636164307	57.90470205	0.16620765	0.532014946
45	0.636452491	58.2750225	0.1709629	0.54865238

46	0.638240232	58.84926406	0.180212157	0.565157187
47	0.640027973	59.42350561	0.192127323	0.569425485
48	0.643633462	59.82844935	0.198317709	0.580330584
49	0.648643577	60.10257205	0.206122841	0.597527253
50	0.653653691	60.37669475	0.212676274	0.614732872
51	0.653922338	60.39669513	0.219226314	0.630485583
52	0.654190984	60.4166955	0.223379421	0.643380665
53	0.657222874	60.48027156	0.228085102	0.653735383
54	0.663830725	60.60023969	0.23749279	0.673943029
55	0.670438576	60.72020782	0.251534632	0.683933297
56	0.674979863	60.75346087	0.263092644	0.699428863
57	0.679217244	60.7739617	0.27420552	0.715200795
58	0.68265319	60.92039418	0.278728141	0.74044451
59	0.684285909	61.35017287	0.284528862	0.758677151
60	0.685918627	61.77995156	0.29123443	0.787295617
61	0.686591799	62.11642507	0.298745538	0.81105458
62	0.686934092	62.42072439	0.305713738	0.844772068
63	0.687565368	62.68240575	0.319709285	0.860189119
64	0.689517707	62.74926218	0.325550635	0.871315338
65	0.691470046	62.81611861	0.331809459	0.885007217
66	0.696886125	63.17359125	0.335124464	0.898300364
67	0.704467042	63.71269902	0.34129593	0.918053963
68	0.711883745	64.25939104	0.350479885	0.933788091
69	0.716262492	64.94639162	0.359060528	0.946742761
70	0.720641238	65.63339219	0.368632278	0.974973159
71	0.725311118	66.09200876	0.375512234	0.991180644
72	0.730287454	66.31022111	0.382475387	1.00885399
73	0.73526379	66.52843345	0.390684364	1.043605521
74	0.741733141	66.82796853	0.396356167	1.079276615
75	0.74832691	67.13428051	0.40249041	1.101180428
76	0.752678911	67.48566791	0.409013986	1.114756503
77	0.753027756	67.91754717	0.420882268	1.141143105
78	0.753376602	68.34942642	0.426383015	1.162120011
79	0.755461418	69.43105669	0.434304392	1.184544405
80	0.757994227	70.68036465	0.441321488	1.230923428
81	0.760371186	71.87864921	0.450976424	1.257246158
82	0.762228645	72.90685582	0.45956105	1.289676885
83	0.764086105	73.93506243	0.472471772	1.307930182
84	0.765616672	74.85288998	0.482581664	1.354532256
85	0.766983794	75.71552799	0.491598671	1.382650721
86	0.768777103	76.49413663	0.500678837	1.429282333
87	0.774299547	76.53748826	0.512852073	1.462859138
88	0.779821992	76.5808399	0.528063164	1.501453554
89	0.7843843	76.86151901	0.539582697	1.528268688
90	0.788123635	77.34562167	0.547404315	1.585376202
91	0.79186297	77.82972433	0.559359602	1.645946186
92	0.794951644	77.86422628	0.566901366	1.704244215
93	0.798023194	77.88689663	0.578600136	1.768111948
94	0.803268253	79.52813461	0.593754561	1.843759203

95	0.811637728	83.49606358	0.609212164	1.926300134
96	0.820007203	87.46399254	0.618909216	2.098060149
97	0.857372891	89.70020562	0.646134562	2.250903694
98	0.900010617	91.62156127	0.672879985	2.414908545
99	0.930622318	93.00099609	0.726058879	2.567521846
100	0.930622318	93.00099609	0.858244726	2.957309988